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THE UNIVERSITY OF ALBERTA

THE REACTIONS OF ACETYLATED  
GLYCALS AND THEIR DERIVATIVES

BY

BERT FRASER-REID

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

JULY 1964

THE UNIVERSITY OF ALBERTA

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## THE UNIVERSITY OF ALBERTA

## FACULTY OF GRADUATE STUDIES

PART I: The Halogenation and Halogenomethoxylation ofAcetylated Glycols

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled

## THE REACTIONS OF ACETYLATED

## GLYCALS AND THEIR DERIVATIVES

submitted by Bert Fraser-Reid M.Sc., in partial fulfilment of the requirements for the degree of Doctor of Philosophy.



# ABSTRACTS

## PART I: The Halogenation and Halogenomethoxylation of Acetylated Glycals

The reaction of D-glucal triacetate with bromine in carbon tetrachloride gave a 2:1 mixture of cis- and trans- 1,2-dibromides having the  $\alpha$ -D-gluco and  $\alpha$ -D-manno configurations respectively, whereas chlorination gave the cis  $\alpha$ -D-gluco isomer as the sole reaction product. Reaction of D-glucal triacetate with bromine or iodine in methanol containing silver acetate ("direct" halogenomethoxylation) gave the trans-adducts, methyl 2-deoxy-2-halogeno- $\beta$ -D-gluco- and  $\alpha$ -D-manno pyranosides in the ratio 1:2 respectively. The "direct" chloromethoxylation gave the corresponding  $\beta$ -D-gluco and  $\alpha$ -D-manno isomers in 41 and 51% respectively; however the cis  $\alpha$ -D-gluco isomer was also produced in 8% yield.

In the case of D-galactal triacetate, bromination gave a 1:1 mixture of the cis- and trans- dibromides, i.e. the  $\alpha$ -D-galacto and  $\alpha$ -D-talo derivatives respectively, whereas chlorination gave only the 1,2-cis-  $\alpha$ -D-galacto derivative. "Direct" iodomethoxylation gave only the trans-adducts methyl 2-deoxy-2-iodo- $\beta$ -D-galacto- and  $\alpha$ -D-talo-pyranosides in the ratio 1:4 respectively. With "direct" bromomethoxylation, the corresponding isomers were produced in 37 and 52% respectively, and 11% of the 1,2-cis-  $\alpha$ -D-galacto derivatives was obtained. "Direct" chloromethoxylation gave 53, 8 and 39% of the corresponding  $\beta$ -D-galacto,  $\alpha$ -D-talo and



$\alpha$ -D-galacto derivatives respectively.

Bromination of 3,4-dihydropyran in carbon tetrachloride gave a 1:9 mixture of the cis- and trans- dibromides, while with chlorination the corresponding dihalides were produced in 1:1 ratio, judging from the composition of the products obtained on subjecting the mixture of dichlorides to methanolysis. cis- and trans- Bromomethoxides were obtained in 13 and 87% in the "direct" bromomethoxylation, while in the analogous chloromethoxylation, the percentages of the corresponding compounds were 25 and 75% respectively. "Direct" iodomethoxylation gave only the trans-iodomethoxide.

Methanolysis of the mixtures of dibromides or dichlorides usually proceeded with inversion of the reacting anomeric centres, except in the case of 1,2-trans- $\alpha$ -D-talo dibromide where participation of the axial 2-bromine led to products of retention.

## PART II: The Brominolysis of Carbohydrate Iodides

The brominolysis of methyl 2-deoxy-2-iodoglycopyranoside triacetates under conditions for the Viebock-Zeisel alkoxyl determination was only 10% complete after one week. The rate was accelerated upon addition of silver acetate and titration of the iodate produced in the process showed that the reaction was complete after seven hours. Brominolysis of the 2-iodoglucoside gave a nearly quantitative yield of an equimolar mixture of the enantiomers of 1,3,4,6-tetra-O-acetyl-2,5-anhydro-1-methoxy-D-mannose. These products resulted from migration of



the ring oxygen and treatment with methanolic hydrogen chloride converted both compounds to the dimethyl acetal of 2,5-anhydro-D-mannose. Reduction with sodium borohydride gave 2,5-anhydro-D-mannitol.

With the 2-iodomannoside, migration of the glycosidic methoxyl group to the 2- position led to the formation, in about 20% of 2-O-methyl-D-glucose tetraacetates. The main route of reaction involved trans- elimination of hydrogen iodide from carbons 2 and 3 followed by acetoxybromination to give methyl 3-acetoxy-2-bromo 2-deoxy- $\alpha$ -D-arabino-hexopyranoside triacetate. Reduction with sodium borohydride led to methyl 2-bromo-2-deoxy- $\alpha$ -D-altropyranoside and zinc dust reduction produced methyl 2-deoxy- $\alpha$ -D-erythro-hexopyranoside-3-ulose diacetate.



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TABLE OF CONTENTS

Abstracts	iii
Acknowledgements	vi
List of Tables	x
List of Plates	xi
List of Figures	xii
General Introduction	1
<u>PART I: The Halogenonation and Halogenomethoxylation</u> <u>of Acetylated Glycals</u>	2
Introduction	3
Experimental	17
A. Methods and Materials	17
B. Typical Halogenomethoxylations of Acetylated Glycals	20
C. Reactions of D-Glucal Triacetate	23
D. Reactions of D-Galactal Triacetate	38
E. Reactions of 3,4-Dihdropyran	52
Discussion of Results	68
Bibliography	90
<u>PART II: The Brominolysis of Carbohydrate Iodides</u>	99
Introduction	100
Experimental	107
A. Methods and Materials	107
B. Exploratory Reactions	107
C. Brominolysis of Iodides	110



D. Brominolysis of Methyl 2-Deoxy-2-iodo- $\beta$ -D-glucopyranoside Triacetate	113
E. Brominolysis of Methyl 2-Deoxy-2-iodo- $\alpha$ -D-mannopyranoside Triacetate	125
Discussion of Results	136
Bibliography	151



# LIST OF TABLES

## PART I - The Halogenation and Halogenomethoxylation of Acetylated Glycals

		Page
Table I	N.M.R. Analysis of Methyl 2-Deoxy-2-Halogeno- $\beta$ -D-gluco- and $\beta$ -D-galactopyranoside Triacetates	64
Table II	N.M.R. Analysis of Methyl 2-Deoxy-2-Halogeno- $\alpha$ -D-manno- and $\alpha$ -D-talopyranoside Triacetates	65
Table III	N.M.R. Analysis of Methyl 2-Bromo-2-deoxy- $\beta$ -D-mannopyranoside Triacetate and Methyl 2-Chloro-2-deoxy- $\alpha$ -D-galactopyranoside Triacetate	66
Table IV	Stereochemical Routes of Reaction	67

## PART II - The Brominolysis of Carbohydrate Iodides

Table I	Reaction of 2-Iodo-glycosides with Bromine	108
Table II	Reaction of 2-Iodo-glycosides with Bromine and Silver Acetate	109



LIST OF PLATESPART I - The Halogenation and Halogenomethoxylation  
of Acetylated Glycals

	Page
Plate I      Reaction Products from D-Glucal Triacetate	22
Plate II      Reaction Products from D-Galactal Triacetate	39
Plate III     Reaction Products from 3,4-Dihdropyran	53



LIST OF FIGURES

(Unless otherwise indicated all Figures are A60 n.m.r. spectra)

PART I: The Halogenation and Halogeno-  
Methoxylation of Acetylated  
Glycals

	Page
Fig. 1a D-Glucal Triacetate	19
Fig. 1b D-Galactal Triacetate	19
Fig. 1c 3,4-Dihydropyran	19
Fig. 2a Bromination Products from D-Glucal Triacetate	24
Fig. 2b Bromination Products from D-Galactal Triacetate	24
Fig. 2c Bromination Products from 3,4-Dihydropyran	24
Fig. 3 Products of "Indirect" Bromomethoxylation of D-Glucal Triacetate	26
Fig. 4a Methyl 2-Bromo-2-deoxy- $\beta$ -D-glucopyranoside Triacetate	28
Fig. 4b Methyl 2-Bromo-2-deoxy- $\beta$ -D-mannopyranoside Triacetate	28
Fig. 4c Methyl 2-Bromo-2-deoxy- $\alpha$ -D-mannopyranoside Triacetate	28
Fig. 5a Products from "Direct" Bromomethoxylation of D-Glucal Triacetate	30
Fig. 5b Products from "Direct" Chloromethoxylation of D-Glucal Triacetate	30
Fig. 5c Products from "Direct" Iodomethoxylation of D-Glucal Triacetate	30
Fig. 6a Chlorination Products from D-Glucal Triacetate	32
Fig. 6b Chlorination Products from D-Galactal Triacetate	32
Fig. 6c Chlorination Products from 3,4-Dihydropyran	32
Fig. 7a Methyl 2-Chloro-2-deoxy- $\beta$ -D-glucopyranoside Triacetate	34
Fig. 7b Methyl 2-Chloro-2-deoxy- $\alpha$ -D-mannopyranoside	34



	Page
Fig. 7c Methyl 2-Chloro-2-deoxy- $\alpha$ -D-mannopyranoside Triacetate	34
Fig. 8a Methyl 2-Deoxy-2-iodo- $\beta$ -D-glucopyranoside Triacetate	37
Fig. 8b Methyl 2-Deoxy-2-iodo- $\alpha$ -D-mannopyranoside Triacetate (60 Mc.p.s.)	37
Fig. 8c Methyl 2-Deoxy-2-iodo- $\alpha$ -D-mannopyranoside Triacetate (100 Mc.p.s.)	37
Fig. 9 Methoxy signals at 100 Mc.p.s.	
Fig. 9a Products from "Indirect" Bromomethoxylation of D-Galactal Triacetate	40
Fig. 9b Products from "Direct" Bromomethoxylation of D-Galactal Triacetate	40
Fig. 9c Anomerization of Methyl 2-Bromo-2-deoxy- $\beta$ -D-galactopyranoside Triacetate	40
Fig. 10a Methyl 2-Bromo-2-deoxy- $\beta$ -D-galactopyranoside Triacetate	42
Fig. 10b Methyl 2-Bromo-2-deoxy- $\beta$ -D-galactopyranoside Triacetate (100 Mc.p.s.)	42
Fig. 10c Methyl 2-Bromo-2-deoxy- $\alpha$ -D-talopyranoside Triacetate	42
Fig. 11a Products from "Direct" Bromomethoxylation of D-Galactal Triacetate	44
Fig. 11b Products from "Direct" Chloromethoxylation of D-Galactal Triacetate	44
Fig. 11c Products from "Direct" Iodomethoxylation of D-Galactal Triacetate	44
Fig. 12a Methyl 2-Chloro-2-deoxy- $\beta$ -D-galactopyranoside Triacetate	47
Fig. 12b Methyl 2-Chloro-2-deoxy- $\alpha$ -D-galactopyranoside Triacetate	47
Fig. 12c Mixture of Methyl 2-Chloro-2-deoxy- $\alpha$ -D-galacto- and - $\alpha$ -D-Talo-pyranoside Triacetates (100 Mc.p.s.)	47



	Page
Fig. 13a Methyl 2-Deoxy-2-iodo- $\beta$ -D-galactopyranoside Triacetate	50
Fig. 13b Methyl 2-Deoxy-2-iodo- $\alpha$ -D-talopyranoside Triacetate	50
Fig. 13c Methyl 2-Deoxy-2-iodo- $\alpha$ -D-talopyranoside (100 Mc.p.s.)	50
Fig. 14a Products from "Indirect" Bromomethoxylation of Dihydropyran	55
Fig. 14b Products from "Indirect" Bromomethoxylation of Dihydropyran in Polar Medium	55
Fig. 14c Products from "Indirect" Chloromethoxylation of Dihydropyran	55
Fig. 14d Products from Methanolysis of <u>trans</u> -2,3-Dichlorotetrahydropyran	55
Fig. 15a Products from "Direct" Bromomethoxylation of Dihydropyran	57
Fig. 15b Products from "Direct" Chloromethoxylation of Dihydropyran	57
Fig. 15c Products from "Direct" Iodomethoxylation of Dihydropyran	57
Fig. 16a <u>cis</u> - and <u>trans</u> - 2,3-Dichlorotetrahydropyrans	58
Fig. 16b <u>trans</u> -2,3-Dichlorotetrahydropyran	58
Fig. 16c Equilibration of 2,3-Dichlorotetrahydropyrans	58
Fig. 17a <u>trans</u> -2,3-Dichlorotetrahydropyran (100 Mc.p.s.)	60
Fig. 17b-j Decoupling Experiments on <u>trans</u> -2,3-Dichlorotetrahydropyran	61



PART II: The Brominolysis of CarbohydrateIodides

	Page
Fig. 1 Rates of Brominolysis of Methyl 2-Deoxy-2-iodo- $\beta$ -D-gluco- and - $\alpha$ -D-manno-pyranoside Triacetates	111
Fig. 2a Methyl 6-Deoxy-6-iodo- $\alpha$ -D-glucopyranoside Triacetate	113
Fig. 2b Methyl 6-Bromo-6-deoxy- $\alpha$ -D-glucopyranoside Triacetate	113
Fig. 2c Methyl $\alpha$ -D-Glucopyranoside Tetraacetate	113
Fig. 3 Methoxyl signals at 100 Mc.p.s. for Methyl 6-Deoxy-6-iodo- $\alpha$ -D-glucopyranoside Triacetate, Methyl 6-Bromo-6-deoxy- $\alpha$ -D-glucopyranoside Triacetate and Methyl - $\alpha$ -D-glucopyranoside Tetraacetate	114
Fig. 4 Gas Liquid Partition Chromatogram of Products from Brominolysis of Cyclohexyl Iodide	116
Fig. 5a Products from Brominolysis of Methyl 2-Deoxy- 2-iodo- $\beta$ -D-glucopyranoside Triacetate	119
Fig. 5b 1,3,4,6-Tetra-O-acetyl-2,5-anhydro-1-methoxy- $\beta$ -D-mannose	119
Fig. 5c 1,3,4,6-Tetra-O-acetyl-2,5-anhydro-1-methoxy $\alpha$ -D-mannose	119
Fig. 6 The Dimethyl Acetal of 2,5-Anhydro-D-mannose Triacetate	121
Fig. 7 Periodate Oxidation of the Dimethyl Acetal of 2,5-Anhydro-D-mannose	122
Fig. 8 Diglycerol Tetraacetate	121
Fig. 9 2,5-Anhydro-D-mannitol Tetraacetate	121



	Page
Fig. 10 2- <del>O</del> -Methyl-D-glucitol Pentaacetate	127
Fig. 11 Periodate Oxidation of 2-O-Methyl-D-Glucitol	129
Fig. 12 Methyl 2-Bromo-2-deoxy- $\alpha$ -D-altropyranoside Triacetate	130
Fig. 13 Methyl 2-Deoxy- $\alpha$ -D-allopyranoside	130
Fig. 14 Infrared spectrum of Methyl 2-Deoxy- $\alpha$ -D- <u>erythro</u> -hexopyranoside-3-ulose Diacetate	133
Fig. 15 2- <del>O</del> -Methyl-D-Glucose Diethyl Dithioacetal	135



## GENERAL INTRODUCTION

The work presented in Part I of this Thesis is concerned with electrophilic addition to D-glucal triacetate and D-galactal triacetate. The stereochemical routes of halogenation and halogenomethoxylation reactions were investigated. In the hope of shedding light on the mechanisms involved in these reactions, the simpler vinyl ether, 3,4-dihydropyran, was investigated. The similarity of some of the results with those from the  $\alpha$ -halogenation of certain cholestanones has been noted.

Part II reports the development of a method to deiodinate 2-iodo-glycosides by means of brominolysis. The products to which these reactions led were established. In an effort to elucidate the mechanism involved, the brominolyses of simpler iodides - a primary iodide (methyl 6-deoxy-6-iodo- $\alpha$ -D-glucopyranoside triacetate), and a secondary iodide (cyclohexyl iodide) were examined.



PART I

The Halogenation and Halogenomethoxylation  
of Acetylated Glycals



## INTRODUCTION

The knowledge that olefins decolourize a solution of bromine in carbon tetrachloride is usually acquired by an organic chemist during his freshman year, and it will no doubt continue to serve him well throughout his professional career since this is one of the most rapid diagnostic tests for suggesting the presence of an olefin. Organic chemistry was still in its infancy when it was discovered (1, 2) that unsaturated compounds could undergo acid-catalysed additions, and, although it was several years before these analogous reactions were recognized as belonging to the same general category of electrophilic reactions (3), their contribution to the development of organic chemistry is enormous. Thus Markownikoff (4) advanced his famous rule concerning the course of addition to olefins in 1870, and the interest it initially attracted (5) has been sustained (6-10) and investigators still find it valuable from the mechanistic (11-13) as well as the synthetic (14-18) standpoint.

The addition of halogens to olefins may be photochemically induced (19,20), but the "dark" reactions were suspected to be heterolytic in nature (21,22) when it was observed that they were sensitive to polar surfaces (23) and polar solvents (24). Thus Francis, (24) isolated the bromiodide and bromochloride when he brominated ethylene in water containing sodium iodide and sodium chloride respectively. When the halogenation was done in a hydroxylic solvent, a halohydrin or its derivative was obtained (25, 26). The diversion of the halide ion by the



incorporation of a competing nucleophile supported the heterolytic process. Thus, the descriptions of halogens as "non-acidic" electrophiles by Ingold (27), is apt since it places them alongside acidic addends in respect to their comparable reactions with unsaturated compounds.

The work of Francis, coupled with the demonstration (28, 29) that the addition of halogens to fumaric and maleic acids produced mainly trans-dihalides, initiated a spate of investigations (30-33) which led to the momentous deduction by Roberts and Kimball (34) that the reactions involved the formation of cyclic halonium ions as the crucial intermediates. Suitable anions in the reaction media, by attacking these ions from the rear, now led to products of trans-configuration. The subsequent refinement of the theory of polar addition to multiple bonds is well catalogued in textbooks (35), and the ability for groups attached to the olefin to influence the process by means of electron delocalisation has been elegantly treated (36).

In 1920, Fischer, Bergmann and Schotte (37) obtained an unstable mixture of "triacetyl glucal dibromides" on bromination of D-glucal triacetate in carbon tetrachloride. Upon methanolysis of the mixture there were obtained two crystalline compounds termed "triacetyl methyl glucoside -2-bromohydrins I and II", for which the  $\beta$ -D-configurations were established by reduction of each with sodium amalgam to methyl 2-deoxy- $\beta$ -D-glucopyranoside. Chlorination of D-glucal triacetate was also suspected to give a mixture since, upon repeated recrystallization of the product, the optical rotation became increasingly positive. Nevertheless, its methanolysis afforded only one "triacetyl methyl glucoside-2-chlorohydrin"



which was assigned a configuration analogous to the "bromohydrin-I" since ammonolysis of either led to the same product, namely "methyl eni-glucosamine".

Reinvestigation of this excellent work was desirable since the configurations at the 2-position of the "bromohydrins I and II" had not been established and recent efforts in this regard were not entirely unequivocal. Manolopoulos, Mednick and Lichtin (38) offered a proof based on the comparative rates of the iodide-catalyzed deoxymercuration of trans-2-chloromercuricyclohexylmethoxide versus the methyl 2-acetoxymercuri-2-deoxyglycosides obtained on reacting D-glucal triacetate with methanolic mercuric acetate. The brominolysis of the acetoxymercuriglycosides was assumed to yield the bromohydrins of related configuration.

However, a less controversial proof seemed desirable in view of the differing opinions on (a) the steric course of methoxymercuration (39-46), (b) the structure of their reference compound (42, 43, 44) and, in addition, (c) the contention (47) that the compound characterized by them (38) as methyl 2-acetoxymercuri-2-deoxy- $\beta$ -D-mannopyranoside triacetate in fact has the  $\alpha$ -D manno configuration.

In another attempt Akagi, Tejima and Nakamura (48) repeated Fischer's synthesis, and treated the deacetylated "bromohydrin I" (a) with benzaldehyde and (b) with sodium methoxide to give "the known methyl 4,6-O-benzylidene-2,3-anhydro- $\beta$ -D-glucopyranoside.\* In this way the halogen on carbon-2 and the hydroxyl on carbon-3 were demonstrated to be in trans relationship. Sodium amalgam reduction of the reaction mixture, as in Fischer's experiments gave methyl 2-deoxy- $\beta$ -D-glucopyranoside only. Akagi and coworkers (48) concluded that the "bromohydrins I and II"

\* The authors probably meant mannopyranoside (50, 51).



differed only at carbon-2 and hence the "bromohydrin II" had the  $\beta$ -manno configuration. The establishment in 1939 (49) of the structure of "methyl epi-glucosamine" as methyl 3-amino-3-deoxy- $\beta$ -D-altropyranoside, required the "bromohydrin I" to possess the gluco-configuration, since the formation of the intermediate methyl 2,3-anhydro- $\beta$ -D-mannopyranoside necessitated the "bromohydrin I" to have a 2,3-trans-configuration. The mechanism proposed by these workers (48) involves the formation of cyclic bromonium ions of  $\alpha$ -D-gluco and  $\beta$ -D-manno (LXX and LXIX, respectively) configurations which open to give the trans dibromides XX and XXI (page 68). Methanolysis, it is suggested, proceeds with inversion at the anomeric centres. If this mechanism were correct, the "bromohydrins I and II" would have the  $\beta$ -D-gluco and  $\alpha$ -D-manno configurations respectively, and on sodium amalgam reduction, there would have been obtained - contrary to their own observation as well as that of Fischer and coworkers (37) - both the  $\alpha$  and  $\beta$  anomers of methyl-2-deoxy-D-glucopyranoside. The proposed mechanism is therefore at variance with the experimental observations.

Since the facility of nuclear magnetic resonance spectroscopy for determining detailed structure (52-56) has gained widespread acceptance, especially in carbohydrate chemistry (57-64), it seemed logical to employ it in this instance. In this way, as will be seen, the assignments of Manolopoulos and coworkers (38) were shown to be correct.

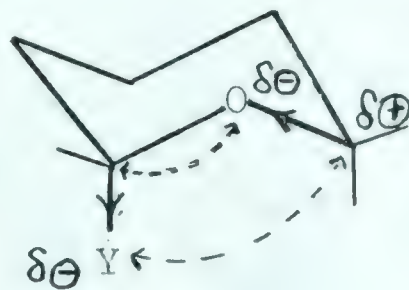
There was interest in these 2-halogenoglycosides as intermediates to other less accessible sugars (58), and their solvolysis products were particularly intriguing. As will be seen in Part II of this Thesis, this fascination was destined to



become more intense during the course of this work (65, 66). In addition, these reactions were of interest from the synthetic standpoint since alteration of the reaction conditions led to vastly different products (57, 58, 67). Thus, addition of the halogen and methoxyl moieties in (a) the manner described by Fischer (37), or (b) via the Prevost reaction (68) as modified by Stanek and Schwarz (69), or (c) by the reaction developed and utilized during this work (58, 67) followed different stereochemical courses. It was therefore of interest to contrast Fischer's two-step synthesis - hereafter described as the "indirect" reaction - with the one-step or "direct" reaction.

The forces accountable for these different reaction pathways were - and in all probability still are - poorly understood, but reactions such as these which involve the anomeric centre, are subject to powerful electronic forces (70, 71) termed the "anomeric effect" which cause polar groups attached to the anomeric centre to favour the axial orientation. The dipole-dipole interaction deemed responsible for this effect is demonstrated by means of arrows in Scheme 1.

dotted lines  
indicate favorable  
coulombic inter-  
actions



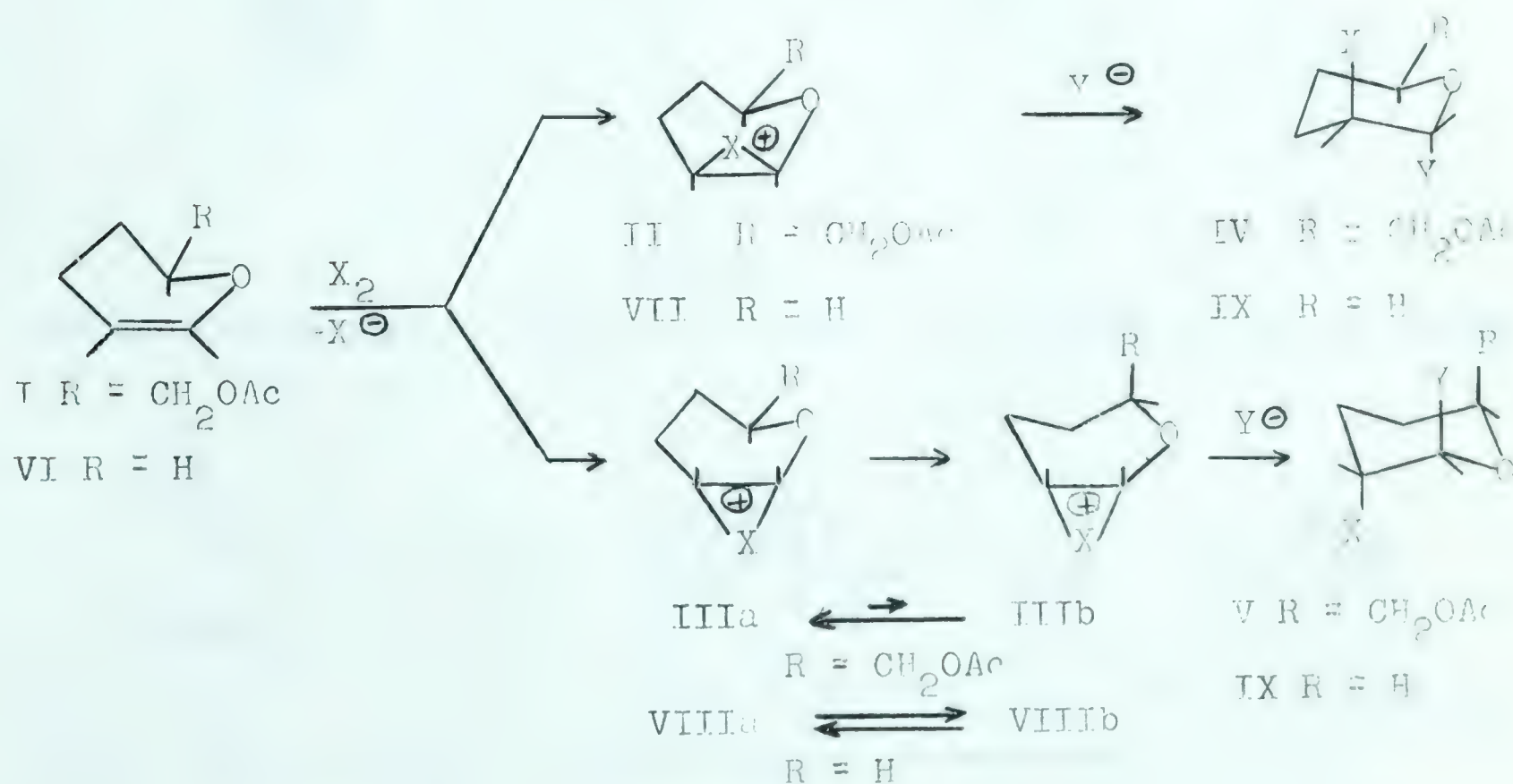
Scheme 1

The tendency for neighbouring halogens to influence reaction pathways is known (72-76) and such participations can lead to diverse results (77-79).

The reaction pathways leading to the methyl 2-deoxy-2-



halogenoglycosides described in this work are of theoretical importance since they involve electrophilic additions to olefins. The "direct" reaction utilizes the common knowledge (80-83) that the addition of a halogen to an olefinic double bond in an hydroxylic solvent yields derivatives of halohydrins along with the dihalide. The inclusion of a silver salt prevents the production of the dihalide through formation of the silver halide. The stereochemical route for these reactions is suggestive of a cyclic halonium ion (34) as an intermediate in the reaction. The favored path of reaction for such cyclic 'onium ions is that leading to trans diaxial adducts and with a vinyl ether such as VI, it can be expected that the nucleophilic attack on the intermediate by the solvent will occur at the carbon bonded to oxygen in view of the possibility of electron release from the oxygen to stabilize the positively charged site of reaction (34).

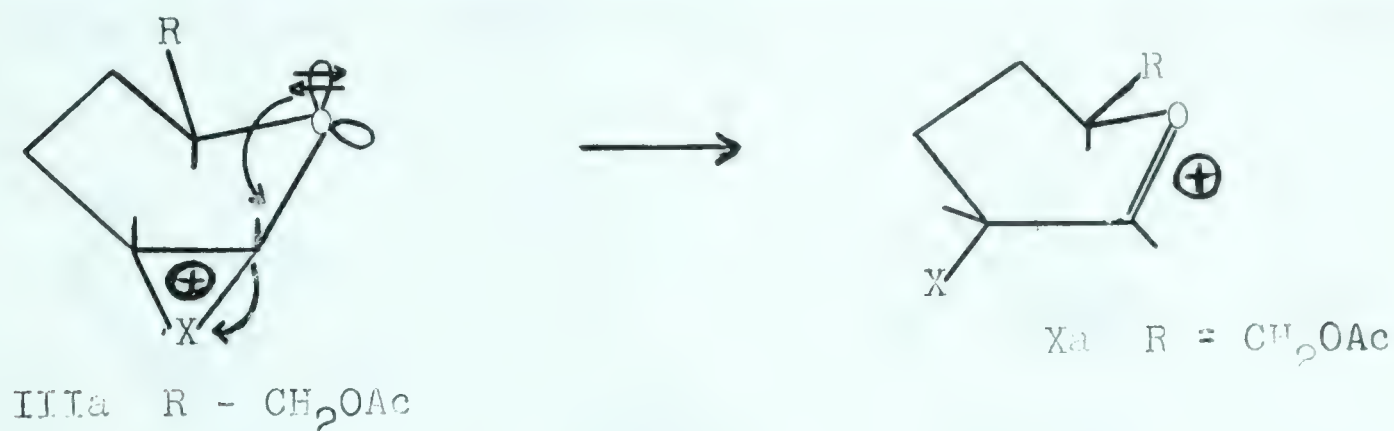


Scheme 2



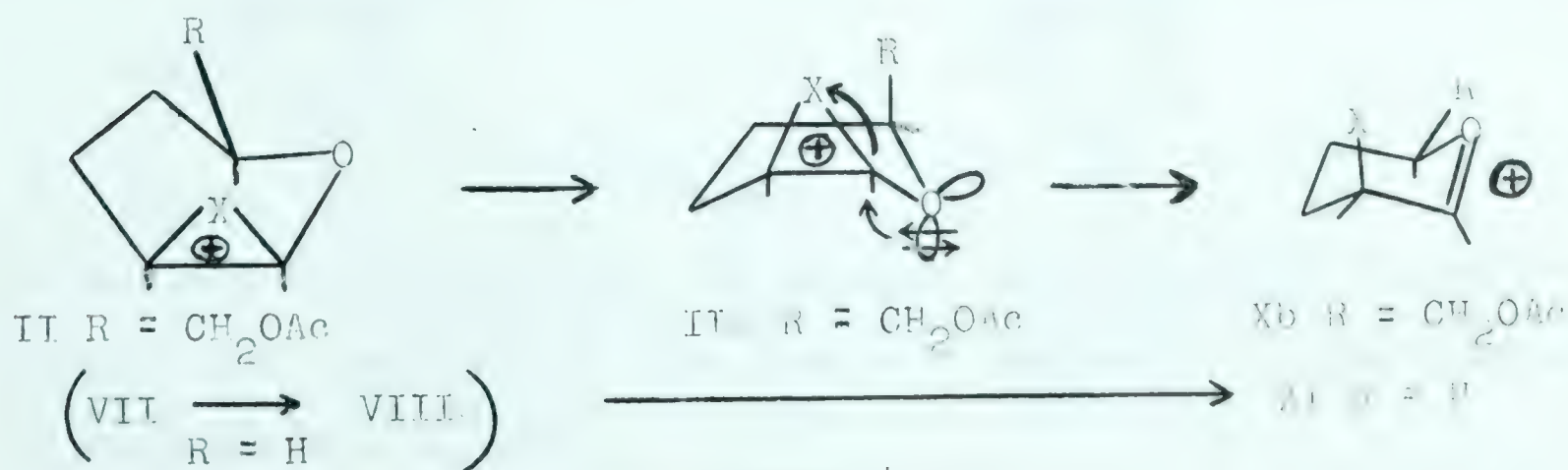
Attack on II leading to the 1,2-trans-adduct IV is favorable (85-88), but in order to open in the diaxial mode, the ion IIIa would have to be converted to IIIb prior to attack leading to V. However, equatorial substituents, particularly the bulky acetoxy-methyl group in the hexopyranoses, makes the interconversion of IIIa to IIIb an unfavorable process. On the other hand, with a conformationally mobile system such as 3,4-dihydropyran (VI), the interconversion of VIIIa to VIIIb is a facile process. In fact attack by the nucleophile at the reacting anomeric centres in either VII  $\rightleftharpoons$  VIIIb or VIIIa leads to IX.

Oxocarbenium ions such as X might conceivably be reaction intermediates. Electron release from the "axial" p-orbitals on the lactol-ring oxygen (Scheme 3) would be in the nature of a trans



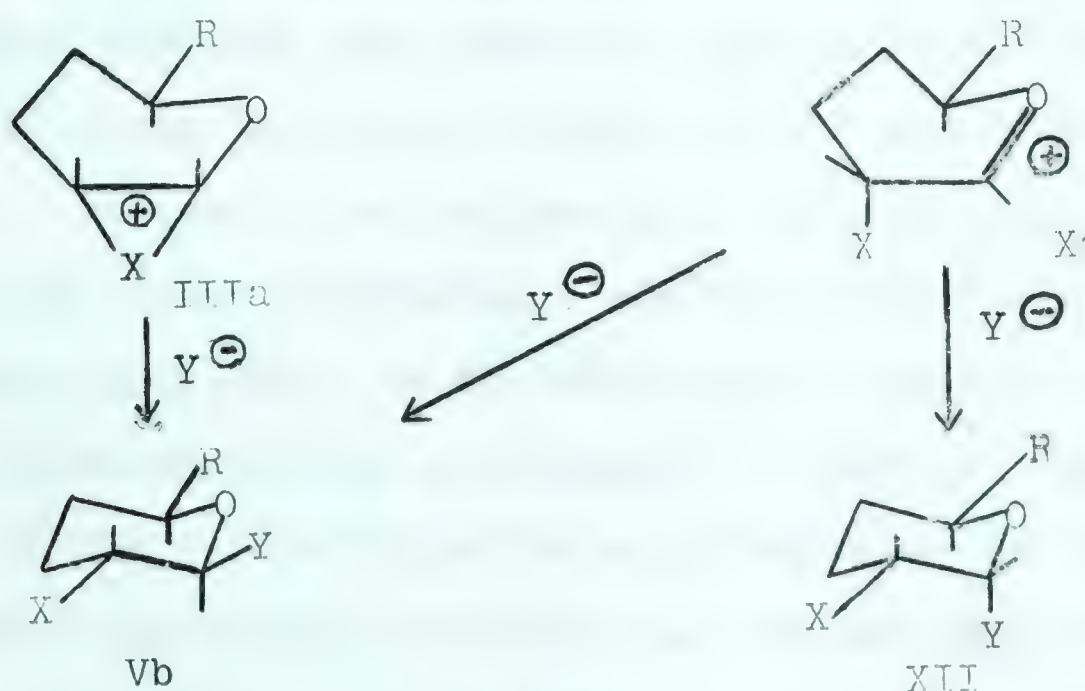
Scheme 3

diaxial elimination. Thus IIIa would be converted to Xa, in which





the substituent halogen is destined to become equatorially oriented. An analogous interaction with the lactol ring oxygen leading to Xb in which the halogen is destined to become axially oriented, presumably requires the preliminary conversion of II to IIa, (Scheme 4). Because of the anchoring effect of the acetoxymethyl group, IIa is highly unfavorable. However, as with the transformations described in the preceding paragraph, the mobile system of 3,4-dihydropyran permits the conversion of VII, which is unfavorable for p-orbital overlap, to its mirror image (VIIIa) and thence to XI. Unfavorable boat intermediates might in this way be precluded. Thus the nature of the cationic species depends on the counterplay of a number of stereoelectronic forces, and ions such as II and X contribute in varying extents to the intermediate equilibrium mixture. Their relative importance will be expected



Scheme 5

to reflect the capacity of the halogen to accommodate a positive charge (90), and this in turn should be reflected in the composition of the reaction product.

As mentioned above, cyclir ions (such as IIIa) should



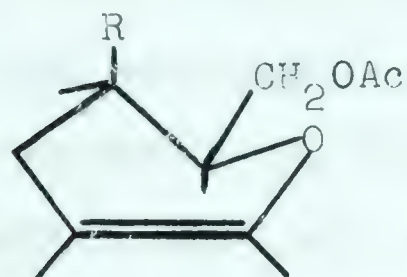
preferentially open to give trans derivatives (such as Vb). whereas an oxocarbonium ion such as Xa, being subject to attack from **either** side, would lead both to cis- and trans-adducts, Vb and XII respectively. This possibility warranted consideration since several instances of cis-addition in electrophilic reactions have come to light; and although most of these examples have been observed with rigid systems (91-96), examples from unstrained systems are frequently encountered (97-102). In addition, it is known (102, 103) that the various halogens behave differently in electrophilic addition.

In view of the foregoing discussions some guidance was sought from the analogous reactions of 3,4-dihydropyran. Previous workers had used it to good effect as a model in carbohydrate reactions (71, 104-112) and its halogenation reactions have been extensively investigated (113-122). Chlorination, which gives the most stable dihalide was reported (122) to yield "one geometric form only" since the product exhibited a "lack of boiling point spread". However, the similarity of physical constants is not unusual for isomeric compounds, and the absence of melting point depression (123, 124), or the sharpness of boiling point (125, 126), cannot always be invoked as criteria of purity. Indeed the constant failure of the latter criterion was a nuisance in this investigation. The further conclusion of Crombie and Harper (122) that this "one geometric form" had the trans-configuration was based on the premise (127) that halogen addition to olefins "is known to occur trans". In the light of the foregoing discussion this conclusion is untenable. In some instances (123) nuclear magnetic resonance was found to be a superior tool for discriminating between isomers; and because of



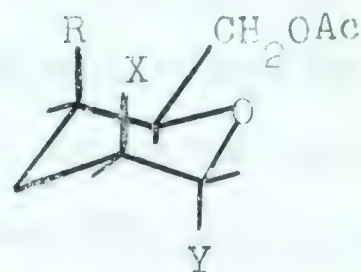
its ability to provide information regarding structural details (52) it seemed desirable to apply it to the problem in question. Recent success of this method in establishing the configuration and conformation of cyclohexene dihalides (128) gave some insight into the behavior to be expected from dihalides of mobile systems.

The foregoing discussion emphasises the electronic forces liable to operate during the reaction. The general indication seems to be that in the absence of other effects, addition to the glycal XIII would lead preferentially to the 1,2-trans-adduct XIV. The



XIII     R = H

XV       R = OAc



XIV     R = H

XVI     R = OAc

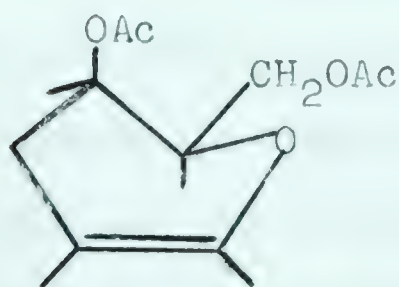
prospect of confronting these electrical forces with a steric effect was intriguing, and for this purpose D-galactal triacetate was quite attractive. The erected acetoxy group at carbon-4 (of XV) should inflict a severe non-bonded interaction on the reaction product XVI. Perhaps the course of the reaction would thereby be altered and hence provide an insight into the intrinsic mechanism of these halogen additions. These reactions are in many respects analogous to the  $\alpha$ -halogenation of ketones in which the formation of an enol-enolate double bond is the crucial step (129-133). It was therefore instructive to consider the course of these well



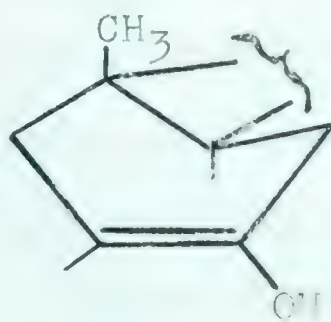
known reactions, and in view of our concern with steric effects, guidance was sought from the extensively investigated  $\alpha$ -halogenation reactions of the cholestanones. The A-ring of cholestan-3-ones, XVII, and the B-ring of cholestan-7-ones, XVIII, were of particular interest since there is some resemblance between the half-chair conformations of their enolic rings and our hindered olefin XV, in spite of the obvious spatial and structural differences. For example, the  $C_{19}$ -CH<sub>3</sub> bond in XVII and XVIII is longer by 0.11Å than the C<sub>4</sub>-O bond in XV (134) and the radius of the methyl group, 2.0Å, is 0.60Å larger than that of oxygen (135). The radius of the oxygen may even be somewhat smaller, since the electrophilic acetyl group may cause the electron density around it to be lessened. However, what was desired in the comparison was not rigid quantitative information, but rather a broad qualitative survey.

The development of theories concerning  $\alpha$ -halogenation of ketones is ably documented elsewhere (136), but evidence to be presented herein seems so challenging that a concise review is considered necessary.

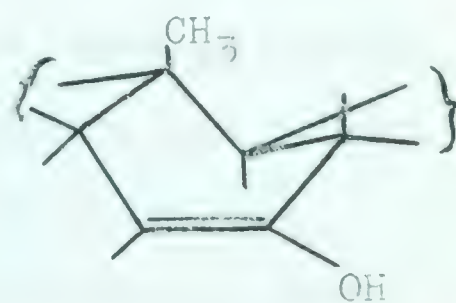
The initial or kinetically-controlled product in the halogenation of these cholestan-3- and -7-ones was postulated to have the halogen axially oriented (137-139). According to Corey (137, 138) this stereoselectivity facilitates the maximum overlap



XV



XVII



XVIII



in the transition state of the positive halogen ion and the p-orbitals of the enol-enolate double bond, thereby affording the lowest energy of activation. In Barton's opinion (85), the reaction might involve a cyclic halonium ion, which undergoes diaxial opening (86, 87) by the halide ion and subsequent elimination of hydrogen halide to give the axial  $\alpha$ -halo-ketone. Either way the formation of the initial product would seem to indicate a preference for axial addition in spite of the disadvantageous interaction with the C<sub>19</sub> methyl group.

It was of interest to see the extent to which these rules would apply to the glycals. If they were found to hold, the formation of products with an axial halogen, at carbon-2 would receive added impetus (see pages 9 and 10). The presence in the reaction medium of hydrogen halide was thought (137, 138) to cause rapid epimerisation so that the product actually isolated is the 2- $\alpha$  - or 6- $\alpha$  -halogen derivative (140). This format seemed in need of some revision (141-143) when Djerassi showed that the sterically unfavorable 2- $\alpha$  -bromo-2- $\beta$  -methyl derivative was produced on bromination of 2- $\alpha$  -methylandrostan-17- $\beta$  ol-3-one acetate (141), for this implied that the halogen had added from the underside to become equatorially oriented in the product.

Since epimerisation of the  $\alpha$ -halo ketone is acid catalyzed, the incorporation of a buffer in the reaction medium forestalls equilibration (144) and therefore permits the inspection of the initially formed products. This approach was especially relevant since these epimerisation-inhibiting con-



ditions may be thought to resemble those for the "direct" halogenomethoxylation reactions. In the latter the halide ions which are necessary for equilibration reactions in halogenations (85, 145-147) are removed as silver halide precipitates. Furthermore, the fact that the mixture obtained on bromomethoxylation of D-galactal triacetate (see experimental section D-II) was not altered by prolonged standing (24 hours) in the reaction medium, demonstrated that the reaction was under kinetic control; if this were not the case, the sterically unfavorable methyl 2-bromo-2-deoxy- $\alpha$ -D-talopyranoside triacetate, XLIII, ought to have been converted to the corresponding galactoside.\*

In an elegantly conceived investigation Warnhoff (123) was able to examine the initially formed gem-2,2-dihalo derivatives on bromination and chlorination of 2- $\alpha$ -bromo or 2- $\alpha$ -chloro-cholestan-3-ones. One might incline to the view that because of its greater bulk there would be more sensitivity on the part of bromine to the presence of the angular methyl group. However, the differences in product composition were considered to be sufficiently insignificant to permit the suggestion (123) that "the steric effects of chlorine and bromine are comparable". The general conclusion was drawn by Warnhoff that the "entering halogen attacks the enol-enolate predominantly from the less hindered  $\alpha$ -side" and consequently becomes equatorially oriented in the product. This

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\* It is reported, for example, that methyl 2-bromo-2-deoxy- $\beta$ -D-mannopyranoside triacetate, XXVII, is quantitatively converted to the corresponding glucoside, XXV, by boiling water (38) although the author was unable to effect this transformation.



view therefore accords with the earlier findings of Djerassi (141), and it possesses an intuitive appeal to the sterically minded which the classical theory lacks. The confusion attendant upon these conflicting theories is exacerbated by a more recently concluded investigation (148).

(i) In agreement with Corey's rules and at variance with Warnhoff's observation, Nickon and Castle (148) found that kinetically controlled bromination of cholestan-7-one, XVIII, or 6- $\alpha$ -chlorocholestan-7-one gave a slight excess of the axial (6- $\beta$ ), to the equatorial 6- $\alpha$ -epimer in both cases. On the other hand,

(ii) chlorination of XVIII or 6- $\alpha$ -bromocholestan-7-one gave no evidence of axial addition. Even more surprisingly, the independently prepared 6- $\beta$ -chloroketone was unchanged after standing for twenty-four hours in chloroform containing twelve times the concentration of hydrochloric acid that would have been produced on complete chlorination of XVIII.

(iii) In agreement with (ii), chlorination of 6- $\beta$ -fluorocholestan-7-one gave no axial chloroketone but, in contrast to (i), its bromination product showed a predominance of the equatorial epimer.

Obviously, as Miss Castle states (148), "the relative importance of steric and stereoelectronic factors is different for different halogens", and Djerassi's lament that "the general stereochemical picture of the halogenation of keto-steroids is not consistent" (141) seems as appropriate today as it was in 1960.



## EXPERIMENTAL

### A. Methods and Materials

#### I. Methods

All melting points were determined on a heating stage and are uncorrected. The nuclear magnetic resonance (n.m.r.) spectra were determined, unless otherwise stated, on neat liquids (in the case of the tetrahydropyran derivatives) or in chloroform with Varian A60 or HR 100 spectrometers. The chemical shifts are reported in tau values relative to tetramethysilane used as an internal standard, and double irradiation experiments were done as described hitherto (128).

Unless otherwise stated, the paper chromatograms were made on Whatman No. 1 paper, and developed with butanol-ethanol-water mixture (5:1:4) (149). The zones were detected with the silver nitrate-sodium hydroxide (150), or the permanganate-periodate (151) spray reagents.

Reverse phase chromatography - preparative or analytical - was performed in the manner described by Wickberg (152), Skellysolve B being used as the developing phase.

Chromatographic fractionations were effected by placing the syrup on a cellulose column in the usual manner (153), and irrigated as described in the appropriate sections.

Distillations were done on a spinning band column, and preparative gas-liquid partition chromatography on an Aerograph Autoprep machine.

#### II. Materials

1. D-Glucal triacetate was prepared from tetra-O-acetyl- $\alpha$ -D-glucopyranosyl bromide ( $\alpha$ -acetobromoglucose) (154) by the method of Roth and Pigman (155). After one recrystallization the product was satisfactory for most purposes, but a purer specimen was obtainable



by distillation under high vacuum ( $140^{\circ}$  at 0.05mm). The n.m.r. spectrum is shown in Fig. 1a.

2. D-Galactal triacetate was prepared in a manner similar to D-glucal triacetate. The product was usually a syrup, but upon distillation ( $133^{\circ}$  at 0.05mm) it crystallised spontaneously. For most preparations the syrupy material was satisfactory. The n.m.r. spectrum is shown in Fig. 1b.

3. The 3,4-dihydropyran used was the Eastman technical grade. The n.m.r. spectrum is shown in Fig 1c.

### III. Characterisation of compounds

The methyl 2-deoxy-2-halogenogluco-sides described in this Thesis were previously reported in the literature. Confirmation of their identity was therefore possible from their physical constants and, in some cases, proofs of their structures were provided by n.m.r. analysis. A number of new 2-deoxy-2-halogenoglycosides were prepared from D-glucal triacetate, D-galactal triacetate and 3,4-dihydropyran. Some of these new compounds were obtained in pure crystalline condition, others as chromatographically pure syrups, and still others only as mixtures with other compounds. In all cases, the characterisation of these compounds was achieved by interpretation of the n.m.r. spectra. In a few cases, the conclusions thus reached were substantiated by hydrogenolysis to the known 2-deoxyglycosides. In other instances, the characterisation was achieved by anomerisation of the known anomer under standard conditions. Since these characterisations could leave no doubt as to identity, elemental analyses in some cases were unnecessary.



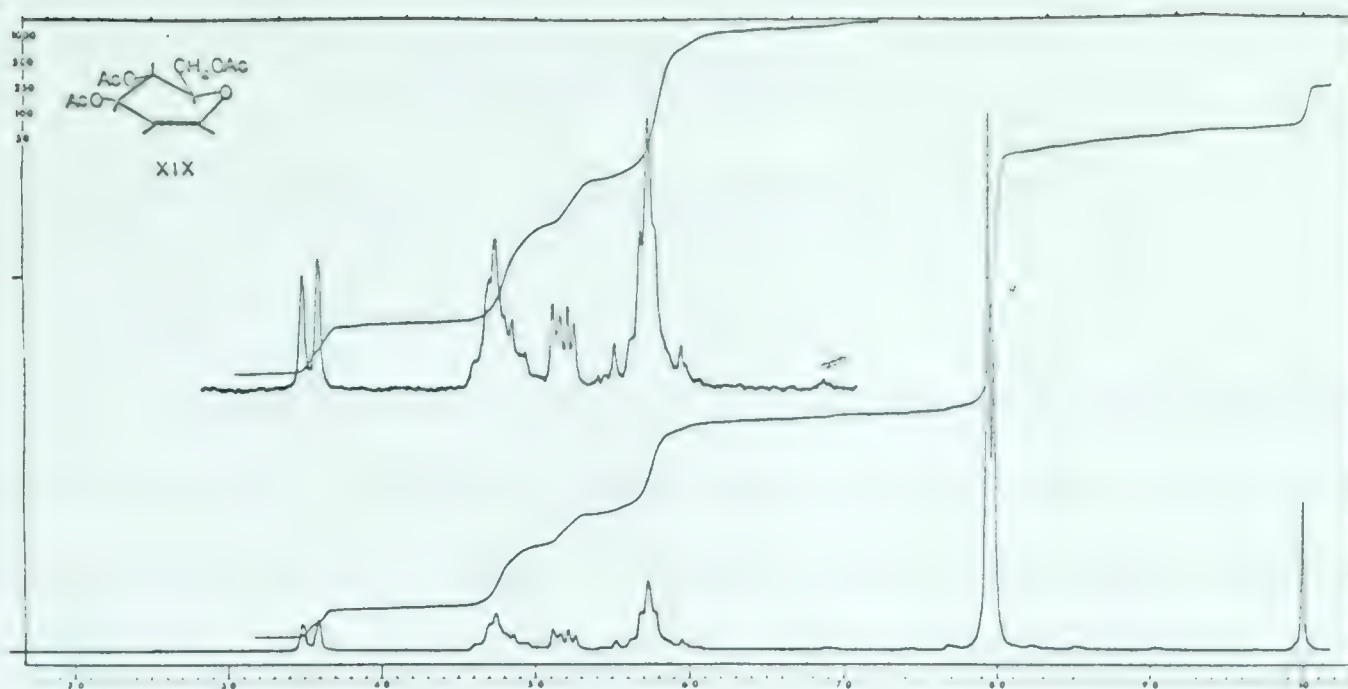


Fig. 1a D-Glucal Triacetate

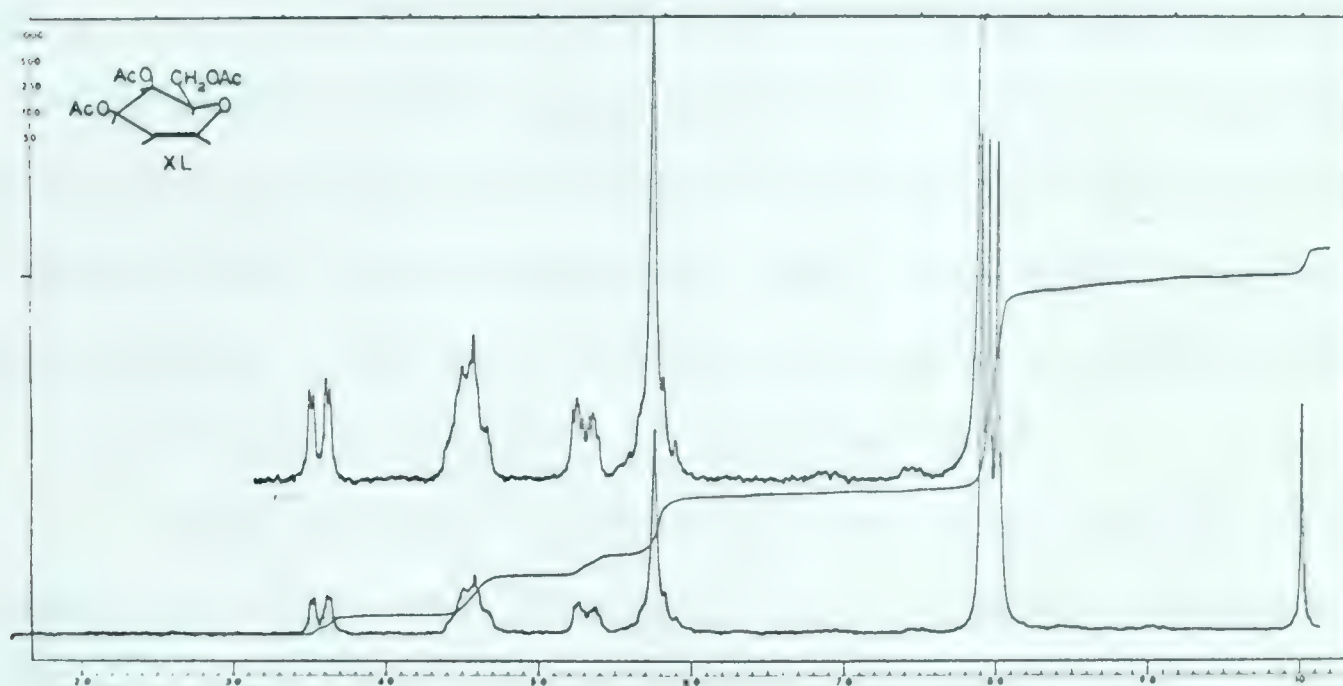


Fig. 1b D-Galactal Triacetate

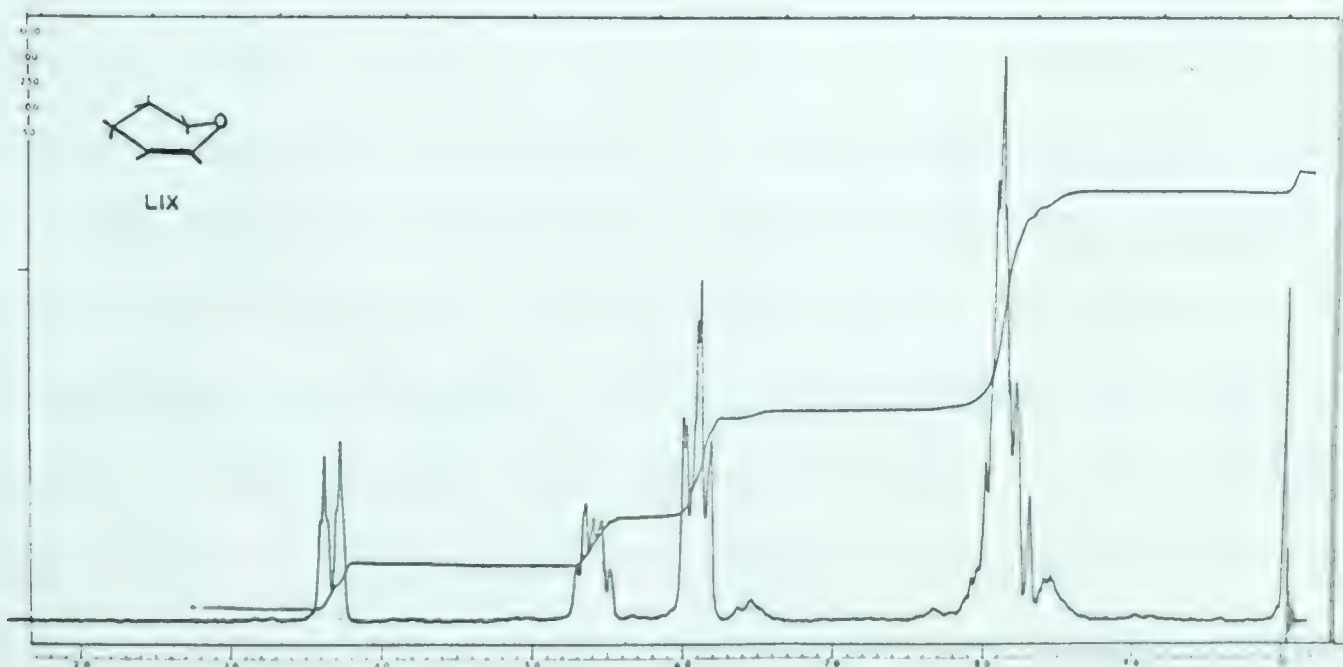


Fig. 1c 3,4-Dihydropyran



B. Typical Halogenomethoxylations of  
Acetylated Glycals

I. "Indirect" Halogenomethoxylations

1. A Typical Halogenation

A stirred solution of 0.026 mole of the acetylated glycal in 50 ml carbon tetrachloride was cooled in an ice bath and protected from light. Bromine was added dropwise, or chlorine was bubbled in, until a colour due to excess halogen was present. After standing for a further fifteen minutes, air was bubbled into the solution to remove the excess halogen, and the solvent was evaporated in vacuo at 40°. In all cases yields were better than 95%, and samples were checked by n.m.r. before and after aeration, evaporation, distillation etc. to ensure that these procedures had not caused rearrangement of the product.

2. A Typical Methanolysis of 1,2-Dihalides

The dihalide, 0.041 mole, was dissolved in 50 ml of dry methanol and after the addition of dry, freshly prepared silver carbonate (0.2 mole), the mixture was stirred until a portion of the filtered reaction mixture failed to give a precipitate with ethanolic silver nitrate - usually 1 to 1.5 hours (118, 156). The silver salts were removed by filtration through Celite, and the filter cake was thoroughly washed before the filtrate was evaporated to dryness. Decolorization of an ethanolic solution with charcoal was usually necessary, and finally a chloroform solution of the product was eluted through a short column of silicic acid. Samples of the product so obtained were analysed by n.m.r. before attempting crystallization, fractionation or



distillation as described in the appropriate sections below.

## II. "Direct" Halogenomethoxylations

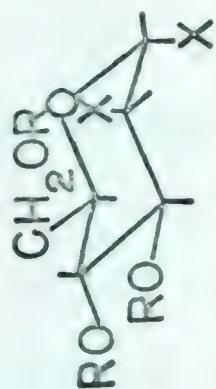
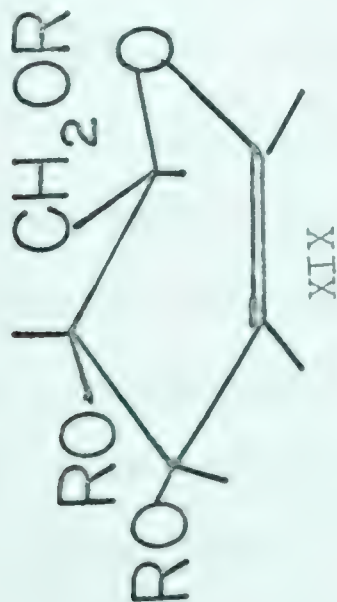
### 1. A Typical Halogenomethoxylation

The glycal (37 mM) was dissolved in 250 ml of dry methanol containing 8.76 g (52 mM) of silver acetate. The mixture was cooled to 0° and 52 mM of bromine or iodine was added over a period of 10 minutes with stirring. In the case of chlorine, the gas was bubbled into the reaction mixture until a starch-iodide paper test on the effluent gases indicated an excess. After an additional 20 minutes the silver salts were removed by filtration and washed with methanol. The filtrate was evaporated in vacuo to a residue which was taken up in chloroform. The chloroform solution was washed with aqueous sodium bicarbonate and sodium thiosulphate solutions, and dried by passage through chloroform-wetted filter paper. Evaporation then produced clear syrups or oils, usually in better than 90% yield and in each case a portion of the material was reserved for n.m.r. analysis prior to attempting isolation or characterization of the components as described below.

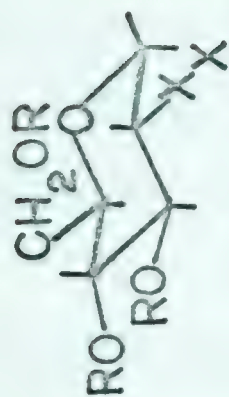
When it was desirable, for example in Part II, to increase the content of the 1,2-trans-adduct ( $\alpha$ -D-manno or  $\alpha$ -D-talo), s-collidine (67 mM) was added to the reaction medium prior to addition of the halogen. The chloroform solution of the syrup from evaporation of the methanol, was washed with water, sulphuric acid (2N), and treated as above beginning with the sodium bicarbonate washing.



Reaction Products from D - Glucal Triacetate

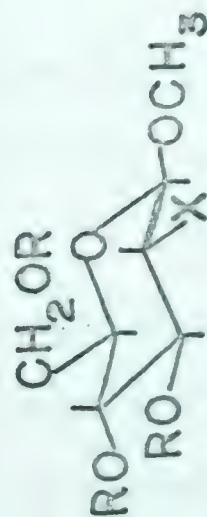


X = Br



X = Br

XXIX X = Cl



R = X = H

XXV R = Ac X = Br

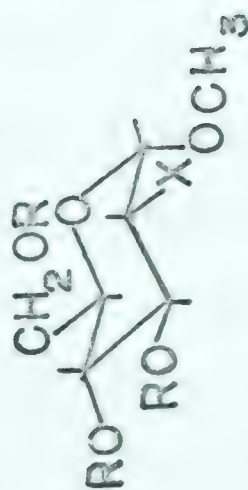
XXVI R = H X = Br

XXX R = Ac X = Cl

XXXI R = H X = Cl

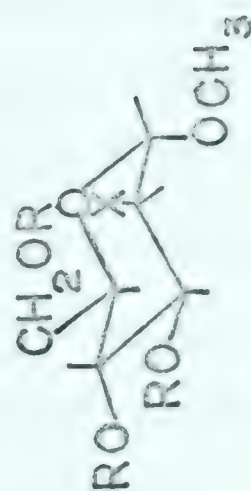
XXXVII R = Ac X = I

XXXVIII R = H X = I



XXXII R = Ac X = Cl

XXXV R = X = H



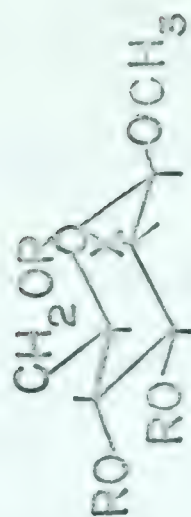
XXXVIII R = Ac X = Br

XXXIII R = Ac X = Cl

XXXIV R = H X = Cl

XXXVIII R = Ac X = I

XXXIX R = H X = I



XXVII R = Ac X = I



## C. Reactions of D-Glucal Triacetate

### I. "Indirect" Bromomethoxylation

1. 2-Bromo-2-deoxy-3,4,6-tri-O-acetyl- $\alpha$ -D-glucopyranosyl Bromide (XXIII) and 2-Bromo-2-deoxy-3,4,6-tri-O-acetyl- $\alpha$ -D-mannopyranosyl Bromide (XXI)

The product of bromination was obtained as a colourless syrup in 95% yield. Two doublets for anomeric hydrogens were present in the n.m.r. spectrum (Fig. 2a) of the product at 3.55 tau (1 c.p.s. spacing) and at 3.53 tau (3.5 c.p.s. spacing). In general, equatorial anomeric hydrogens provide n.m.r. signals of 3 to 4 c.p.s. when coupled to an axial 2-hydrogen (for example in  $\alpha$ -D-galacto-pyranose derivatives Table III) whereas when coupled to an equatorial 2-hydrogen (for example  $\alpha$ -D-manno and  $\alpha$ -D-talo pyranose derivatives, Table II) the observed coupling constant is much smaller, <1 to 1.5 c.p.s. In view of this the compounds XXI and XXIII were assigned the  $\alpha$ -D-manno and  $\alpha$ -D-glucopyranose configurations respectively. The relative intensities of these signals were 1:2, respectively. The total intensity of these two signals as compared to the total intensities of the other signals except for acetyl required the two compounds to comprise more than 90% of the mixture.

In a separate experiment a solution of 1.5 mM of bromine in carbon tetrachloride (0.5 ml) was introduced into a solution of glucal triacetate, 0.13 g (0.5 mM) in carbon tetrachloride (0.5 ml) contained in an n.m.r. tube, and the 3.0 to 4.0 tau region, characteristic for equatorial anomeric protons was scanned within 15 seconds. The experiment was repeated and this time



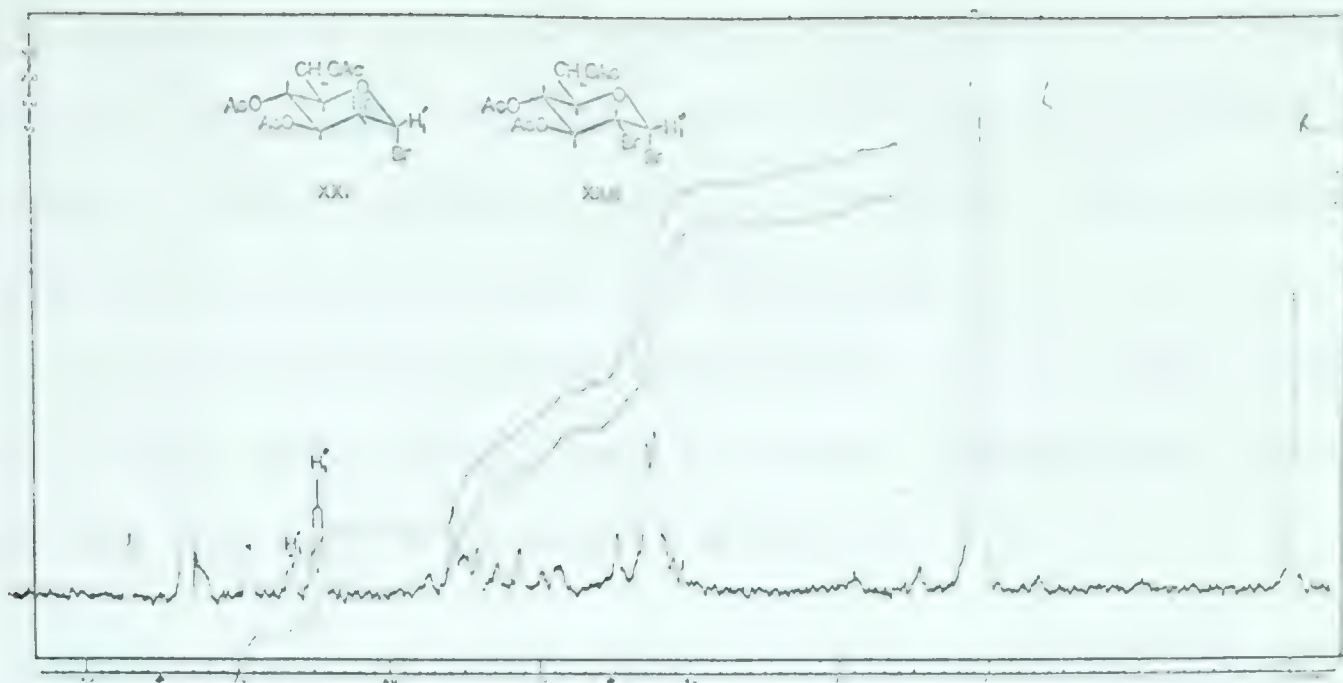


Fig. 2a Bromination Products from D-Glucal Triacetate

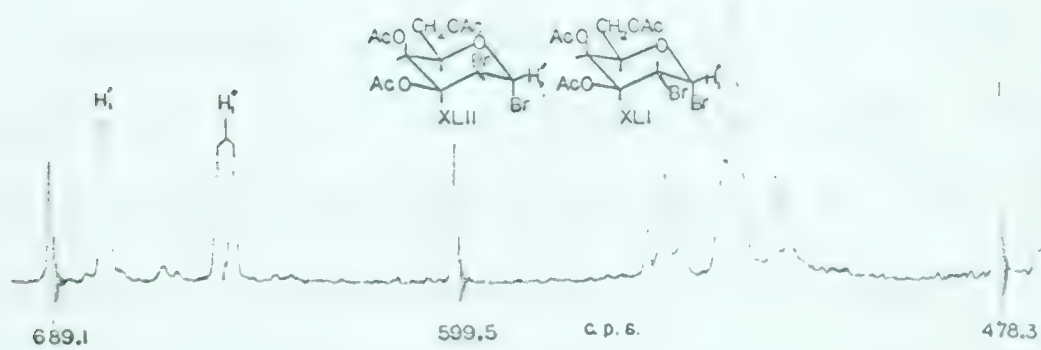


Fig. 2b Bromination Products from D-Galactal Triacetate

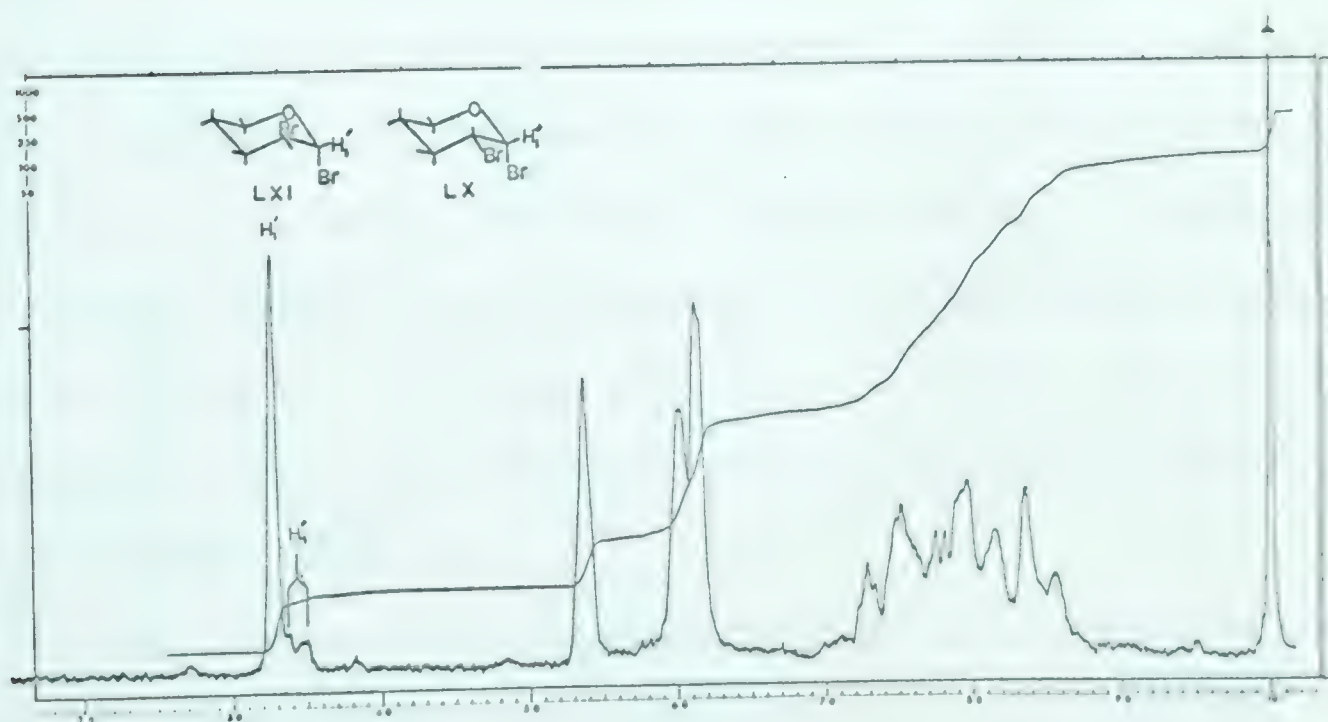


Fig. 2c Bromination Products from 3,4-Dihydropyran



the 4.0 to 5.0 tau region characteristic for axial anomeric protons was scanned. In both cases the spectra were found to be identical with that for the product of the more leisurely experiment. In this way it was shown that  $\beta$  - to  $\alpha$ - anomerisation was not occurring during the reaction.

Repetition of these experiments using a deficiency of bromine gave a like result, and therefore showed that the excess bromine did not have a catalytic effect.

2. Methyl 2-Bromo-2-deoxy- $\beta$ -D-glucopyranoside (XXVI), the Triacetate (XXV) of XXVI, Methyl 2-Deoxy- $\beta$ -D-glucopyranoside (XXIV), and Methyl 2-Bromo-2-deoxy- $\beta$ -D-mannopyranoside Triacetate (XXVII)

The mixture of dibromides (XXI and XXIII) was subjected to methanolysis. The n.m.r. spectrum of the product (Fig. 3) showed three signals for methoxyl groups at 6.40, 6.52 and 6.56 tau with relative intensities of 10:1:1, respectively. A portion of the product, 150 mg, was dissolved in 15 ml of a 10:9:1 mixture of methanol, water and triethylamine, respectively, and reacted with hydrogen in the presence of 5% palladium-on-charcoal. The hydrogen was taken-up within a half hour. After 12 hours, the catalyst was removed by filtration and the bromide ion by stirring with an excess of basic Amberlite IRA-400 resin. Evaporation left a residue which readily crystallized from ethyl acetate in 69% yield (71 mg). The compound, m.p. 121-122°, did not depress the melting point of an authentic sample of methyl 2-deoxy- $\beta$ -D-glucopyranoside, XXIV (58).

The product of methanolysis partially crystallized when dissolved in ethanol to yield compound XXV, m.p. 135-136°,  $[\alpha]_D$



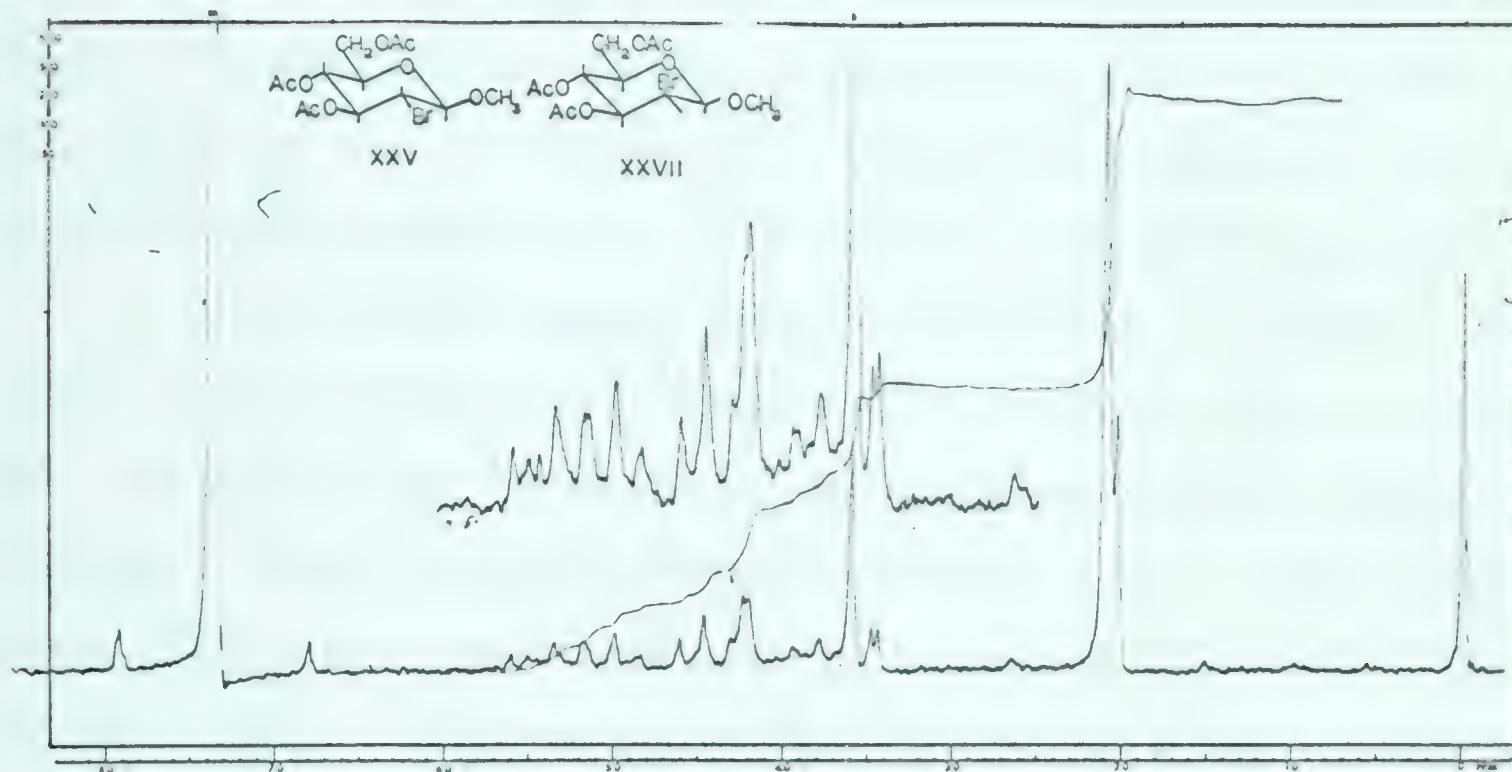


Fig. 3 Products from "Indirect" Bromomethoxylation of D-Glucal Triacetate



46.0° (c, 2 in chloroform) in 26% yield. Reported for "triacetyl methyl glucoside-2-bromohydrin I" (37), m.p. 138°,  $[\alpha]_D$  50.4°.

The n.m.r. spectrum of XXV is reported in Fig. 4a. The assignments shown require the substance to be methyl 2-bromo-2-deoxy- $\beta$ -D-glucopyranoside triacetate wherein the 1- and 2- hydrogens define a dihedral angle of 180° in view of the coupling constant of 9 c.p.s. (52). The substance was formed in considerable yield in view of the intensity of its anomeric signal in the spectrum of the original reaction product.

Deacetylation of XXV in methanolic ammonia provided methyl 2-bromo-2-deoxy- $\beta$ -D-glucopyranoside, XXVI, m.p. 182-184°,  $[\alpha]_D$  0.9° (c, 2.4 in methanol). Fischer and coworkers (37) reported the constants m.p. 179-180° and  $[\alpha]_D$  0.87° for this product.

The mother liquor from the isolation of XXV was deacetylated at room temperature in methanolic ammonia and the product was fractionated by preparative paper chromatography on Whatman 3MM paper using n-butanol-ethanol-water (5:1:4). The chromatogram showed five main components with  $R_f$  values of 0.14, 0.33, 0.49, 0.66 and 0.80. The central zone,  $R_f$  0.49, provided a substance which crystallized on acetylation with acetic anhydride and pyridine. The melting point of the compound XXVII, 110-111° and  $[\alpha]_D$  -89.5° (c, 1.2 in chloroform) were similar to those reported by Fischer and coworkers (37) for their "triacetyl methyl glucoside-2-bromohydrin II", m.p. 115-116°  $[\alpha]_D$  -92.0°. The n.m.r. spectrum of XXVII is shown in Fig. 4b. The chemical shift for the methoxy group is indicative of the  $\beta$ -D-configuration (see Table I), and this is supported by the fact that hydrogenolysis gives the above described methyl 2-deoxy- $\beta$ -D-glucopyranoside. The analysis shown



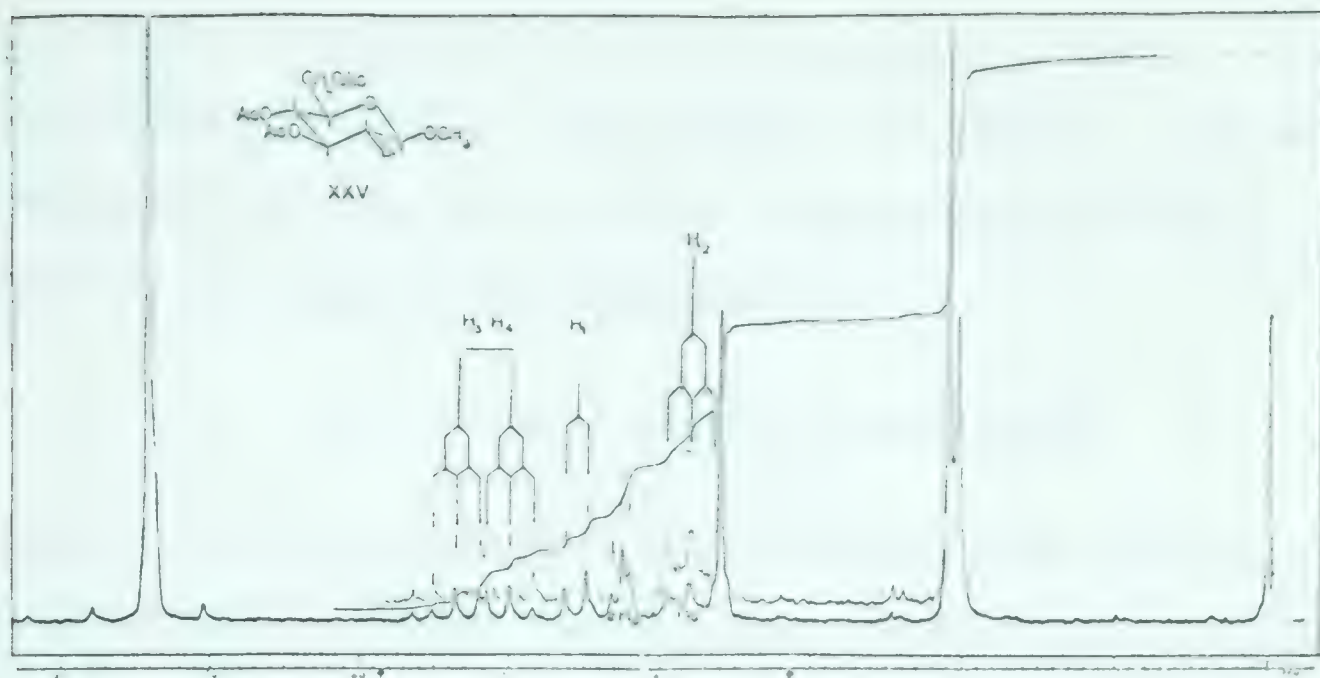


Fig. 4a Methyl 2-Bromo-2-deoxy-β-D-glucopyranoside Triacetate

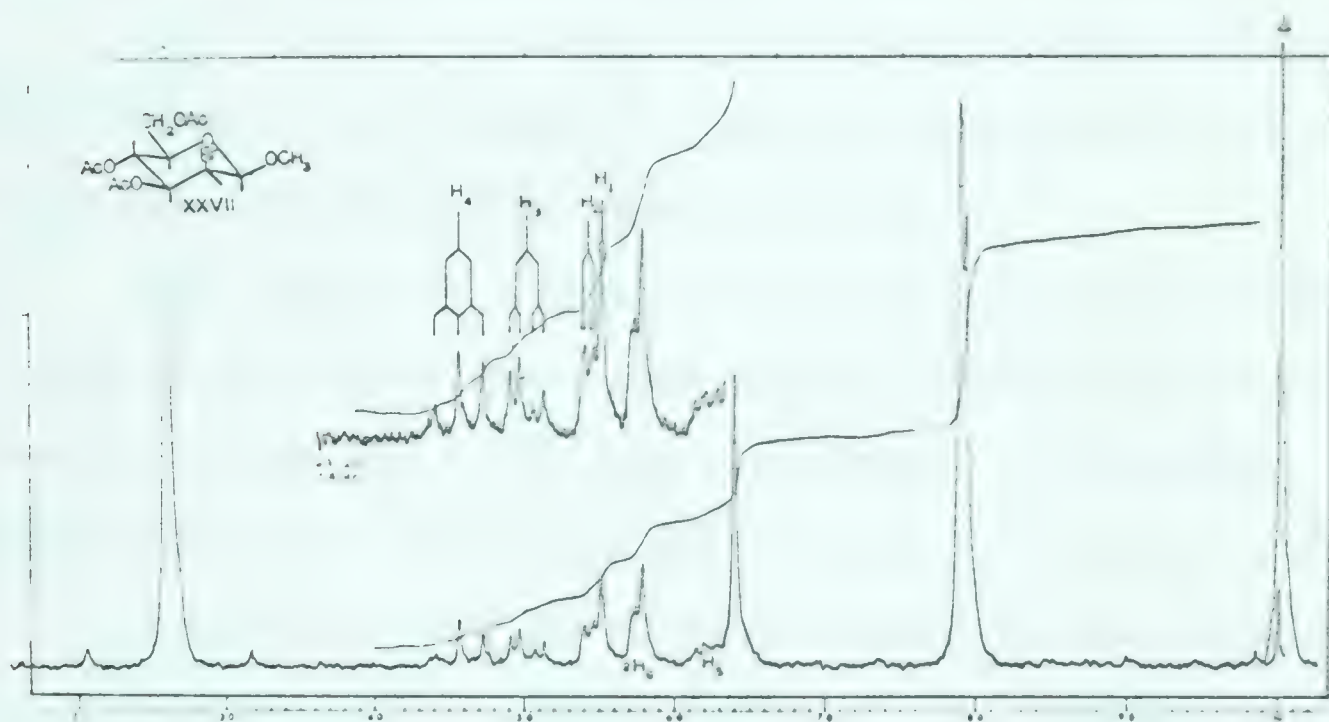


Fig. 4b Methyl 2-Bromo-2-deoxy-β-D-mannopyranoside Triacetate

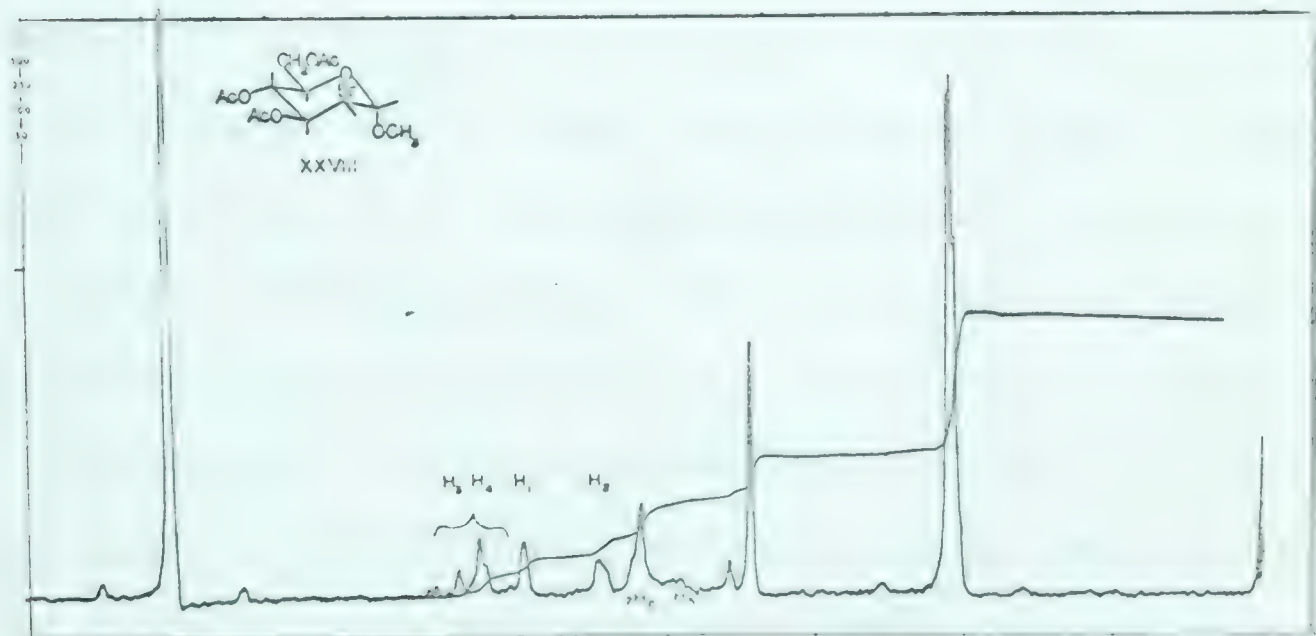


Fig. Methyl 2-Bromo-2-deoxy-α-D-mannopyranoside Triacetate



in Fig. 4 obviously supports its characterization as methyl 2-bromo-2-deoxy- $\beta$ -D-mannopyranoside triacetate, XXVII. The  $R_f$  value of the product formed on deacetylation of XXV was 0.66 and this spot was more intense than that for deacetylated XXVII in the abovementioned preparative chromatogram.

## II. "Direct" Bromomethoxylation

1. Methyl 2-Bromo-2-deoxy- $\beta$ -D-glucopyranoside (XXIV), the Triacetate (XXV) of XXVI, and Methyl 2-Bromo-2-deoxy- $\alpha$ -D-mannopyranoside Triacetate (XXVIII)

The n.m.r. spectrum of the syrupy product contained two signals for methoxyl groups of relative intensities 1:2 at 6.38 and 6.57 tau, respectively (see Fig. 5a).

The syrup was dissolved in ethanol and on cooling a 26% yield of the above described methyl 2-bromo-2-deoxy- $\beta$ -D-glucopyranoside triacetate, XXV, was deposited. The methoxy group of this compound (Fig. 4a) was found to give its signal at 6.38 tau.

A portion, 4.0 g, of the material in the mother liquor of the glucoside, XXV, was deacetylated with methanolic ammonia and chromatographed on a cellulose column using n-butanol saturated with water. The first fraction, 670 ml of eluate, contained 1.45 g of material which after acetylation with acetic anhydride in pyridine proved to be the major product in the reaction mixture, namely, methyl 2-bromo-2-deoxy- $\alpha$ -D-mannopyranoside triacetate, XXVIII, contaminated to an extent of 14% by the  $\beta$ -D-glucose isomer XXV. The specific rotation of the mixture was  $31.2^\circ$  in chloroform ( $c$ , 1.31). The n.m.r. spectrum of this compound, shown in Fig. 4c, bears a close resemblance to that of the 2-chloro analogue



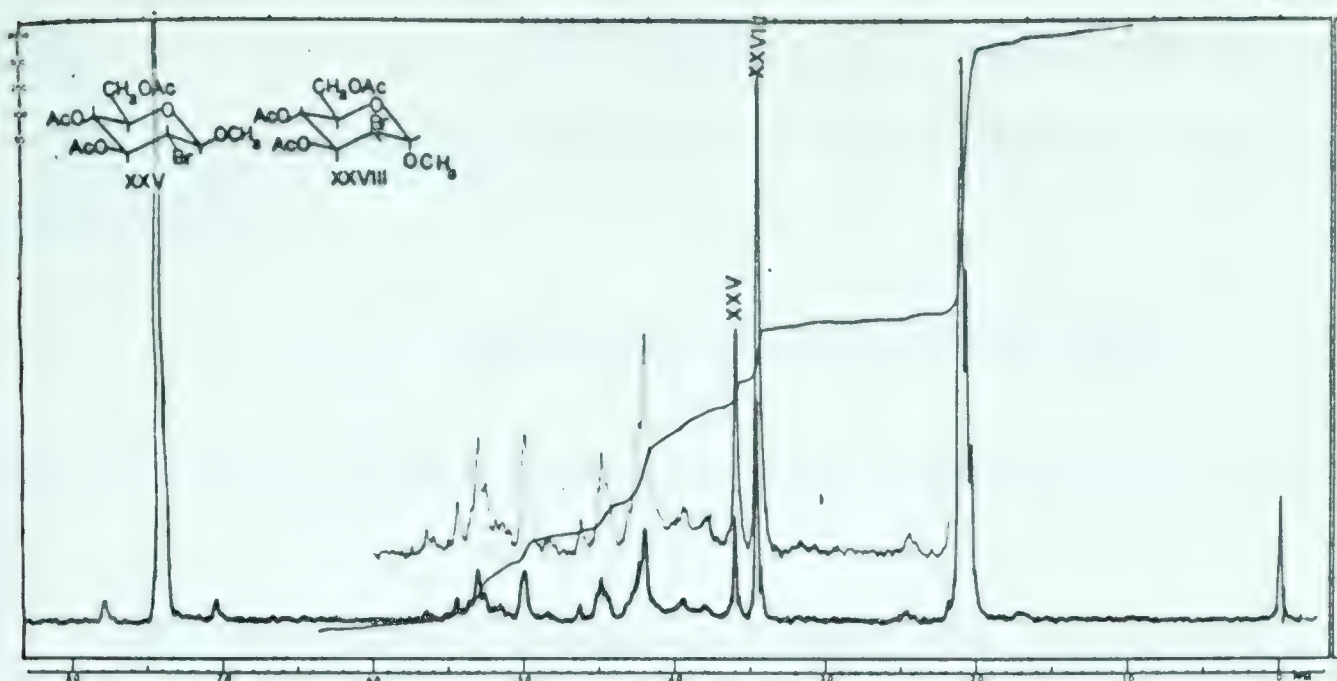


Fig. 5a Products from "Direct" Bromomethoxylation of D-Glucal Triacetate

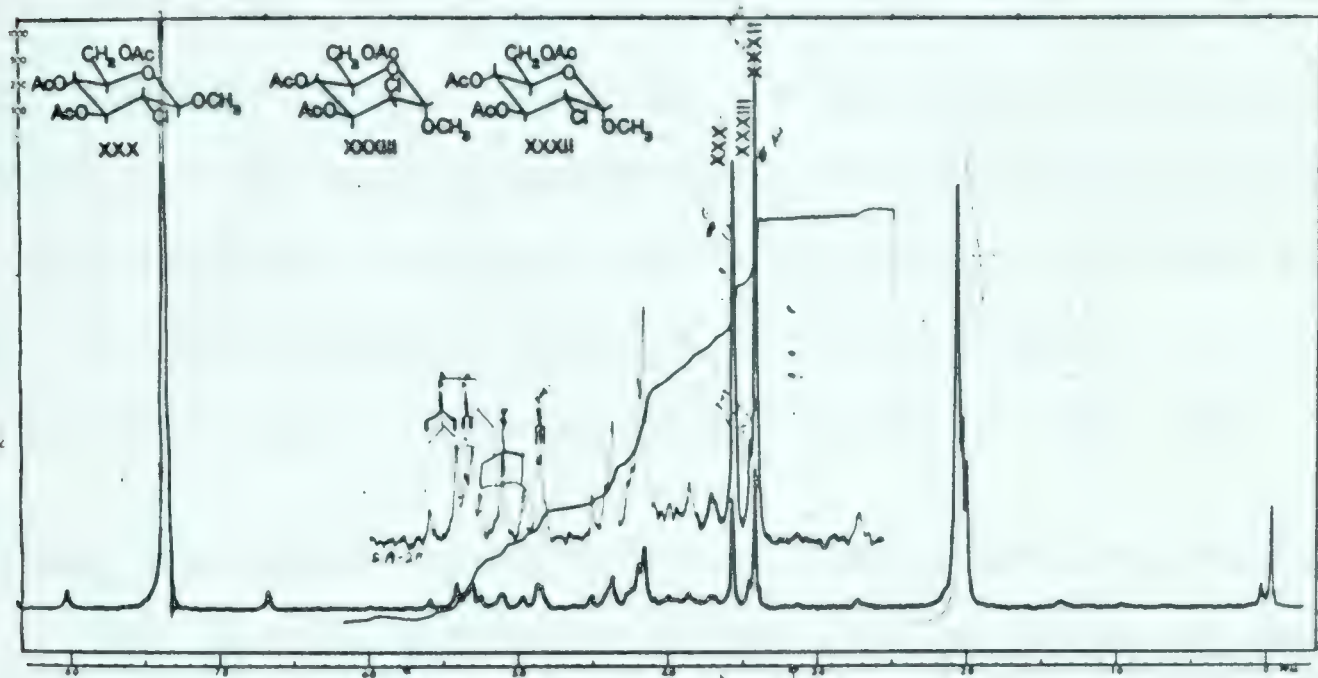


Fig. 5b Products from "Direct" Chloromethoxylation of D-Glucal Triacetate

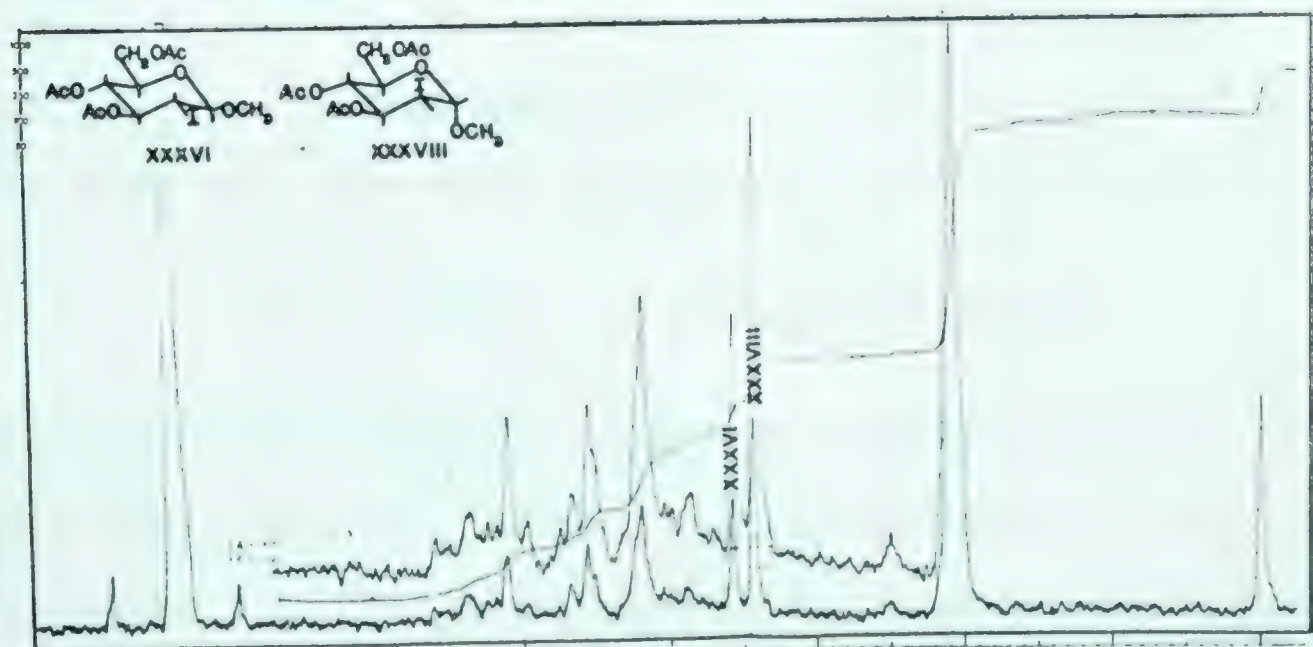


Fig. 5c Products from "Direct" Iodomethoxylation of D-Glucal Triacetate



discussed below in section C-IV, and therefore supports the assignment of structure. Furthermore hydrogenolysis in the usual manner (section C-I) afforded methyl 2-deoxy- $\alpha$ -D-glucopyranoside, XXXV.

### III. "Indirect" Chloromethoxylation

#### 1. 2-Chloro-2-deoxy-3,4,6-tri-O-acetyl- $\alpha$ -D-glucopyranosyl Chloride (XXIX)

Chlorination of D-glucal triacetate gave a 92% yield of a syrup,  $[\alpha]_D$  152.7°; ( $c$ , 1.64 in chloroform). Its n.m.r. spectrum (Fig. 6a) indicated the presence of only one dichloride and the coupling constant (3.5 c.p.s.) for the anomeric proton at 3.74 tau required it to be 2-chloro-2-deoxy- $\alpha$ -D-glucopyranosyl chloride, XXIX. The material resisted crystallization, but after standing in ether solution at room temperature for one week, its n.m.r. spectrum showed that it had undergone no change (cf. 37).

#### 2. Methyl 2-chloro-2-deoxy-3-D-glucopyranoside Triacetate (XXX)

The syrupy dichloride (XXIX) on subjection to methanolysis in the usual manner (section B-I) yielded a syrup (86%) whose n.m.r. spectrum showed XXX as the only methyl glycoside. Crystalline material was readily deposited from ethanol and was indistinguishable from XXX described immediately below.

### IV. "Direct" Chloromethoxylation

1. Methyl 2-Chloro-2-deoxy- $\beta$ -D-glucopyranoside (XXXI), the Triacetate (XXX) of XXXI, Methyl 2-Chloro-2-deoxy- $\alpha$ -D-glucopyranoside Triacetate (XXXII), Methyl 2-Chloro-2-deoxy- $\alpha$ -D-mannopyranoside (XXXIV), and the Triacetate (XXXIII) of XXXIV



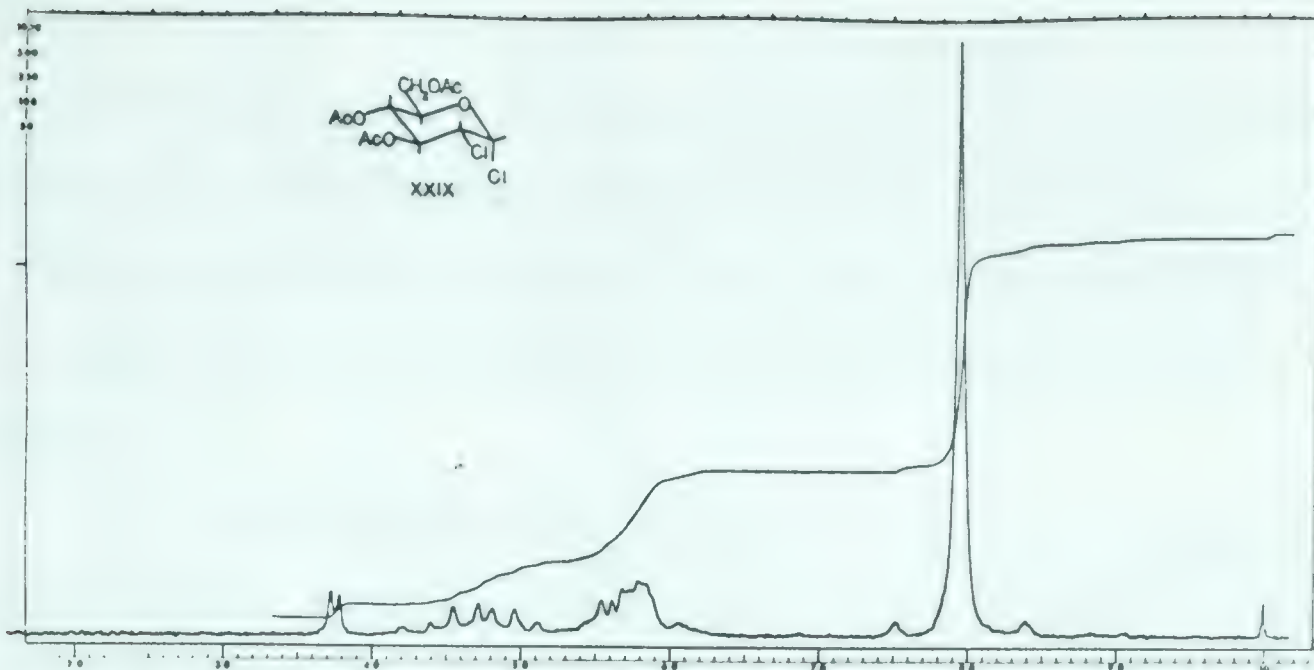


Fig. 6a Chlorination Products from D-Glucal Triacetate

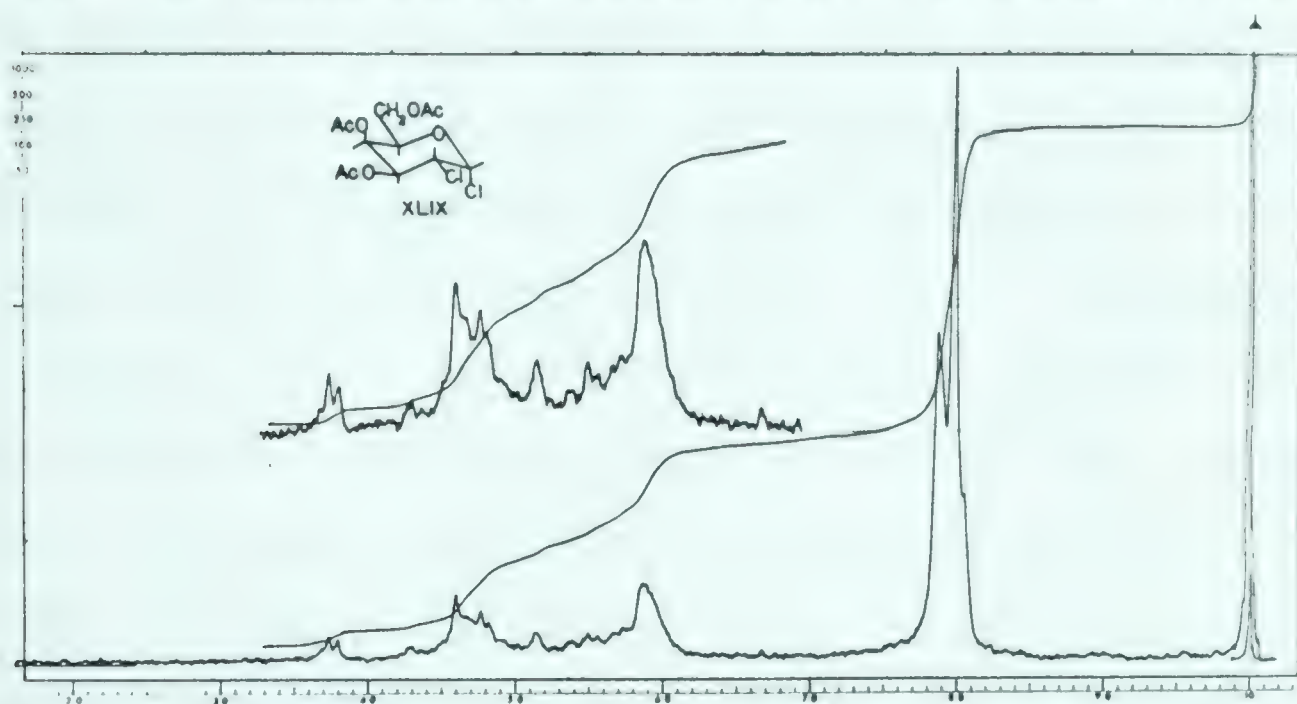


Fig. 6b Chlorination Products from D-Galactal Triacetate

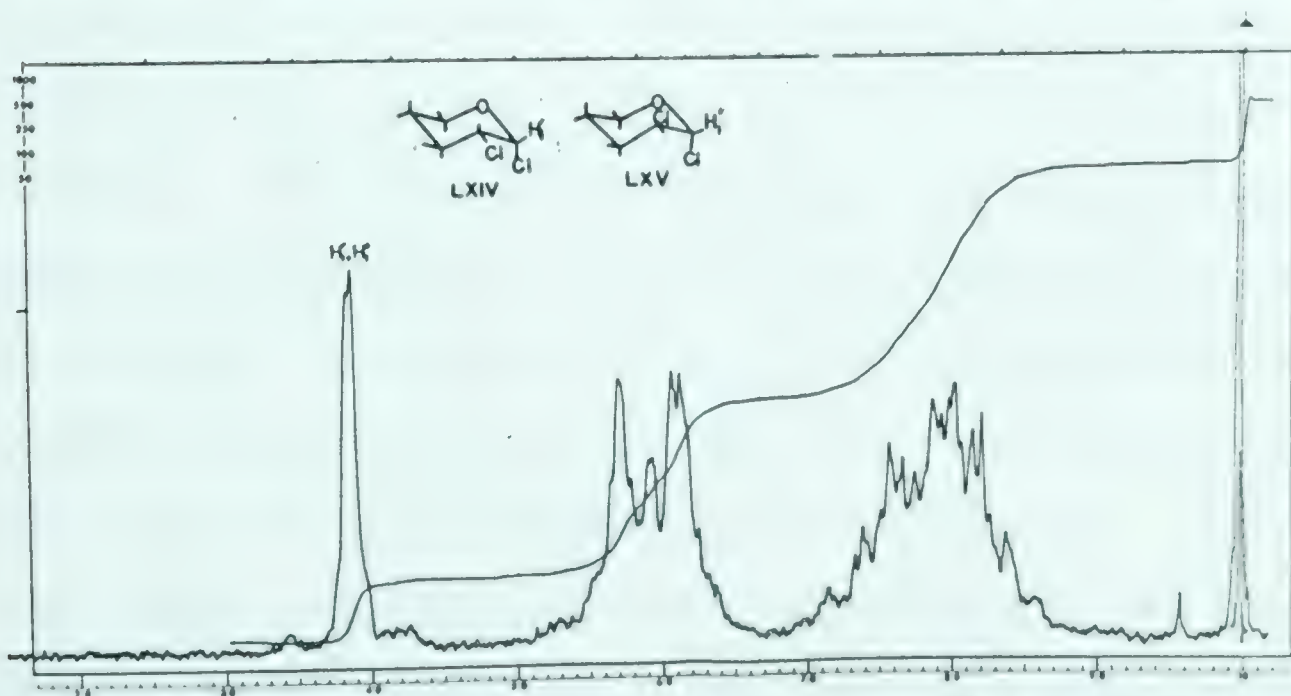


Fig. 6c Chlorination Products from 3,4-Dihydropyran



The A-60 n.m.r. spectrum (Fig. 5b) of the syrupy product obtained on chloromethoxylation of D-glucal triacetate showed the presence of three methyl glycosides as products of the reaction. The signals for the methoxy groups at 6.40, 6.53 and 6.55 tau (XXX, XXXII and XXXIII, respectively) were well resolved at 100 Mc.p.s. and were shown to be in relative amounts 41:8:51, respectively.

On trituration with methanol, 1.23 g of crystalline material (19% from glucal triacetate), m.p. 141-145°, was obtained. After two crystallizations from ethanol, the material possessed physical constants, m.p. 149-150°,  $[\alpha]_D^{25}$  53° (c, 1 in chloroform) and undoubtedly was identical to the "triacetyl methyl glucoside-2-chlorohydrin I" of same melting point and specific rotation 40.2° reported by Fischer and coworkers (37). Deacetylation gave a material, XXXI, of same melting point, 164-165°, and specific rotation in water, -12.9°, as reported (37) for this compound. The n.m.r. spectrum of XXX (Fig. 7a) was very similar to that for the bromine analogue, XXV, shown in Fig. 4a (see also Table I), and therefore required the compound to be methyl 2-chloro-2-deoxy- $\beta$ -D-glucopyranoside triacetate. The substance, 0.51 g, was refluxed with titanium tetrachloride, 0.86 g, in 15 ml of dry chloroform for 15 hours. The product, isolated in the usual manner (157), possessed a specific rotation of 104° in chloroform and its n.m.r. spectrum required the presence of the starting material and a second methyl glycoside with the signal for the methoxy group at 6.53 tau, in the relative amounts 1:2 respectively. The latter substance, XXXII, was also the minor component of the chloromethoxylation product (Fig. 5b), namely methyl 2-chloro-2-deoxy-



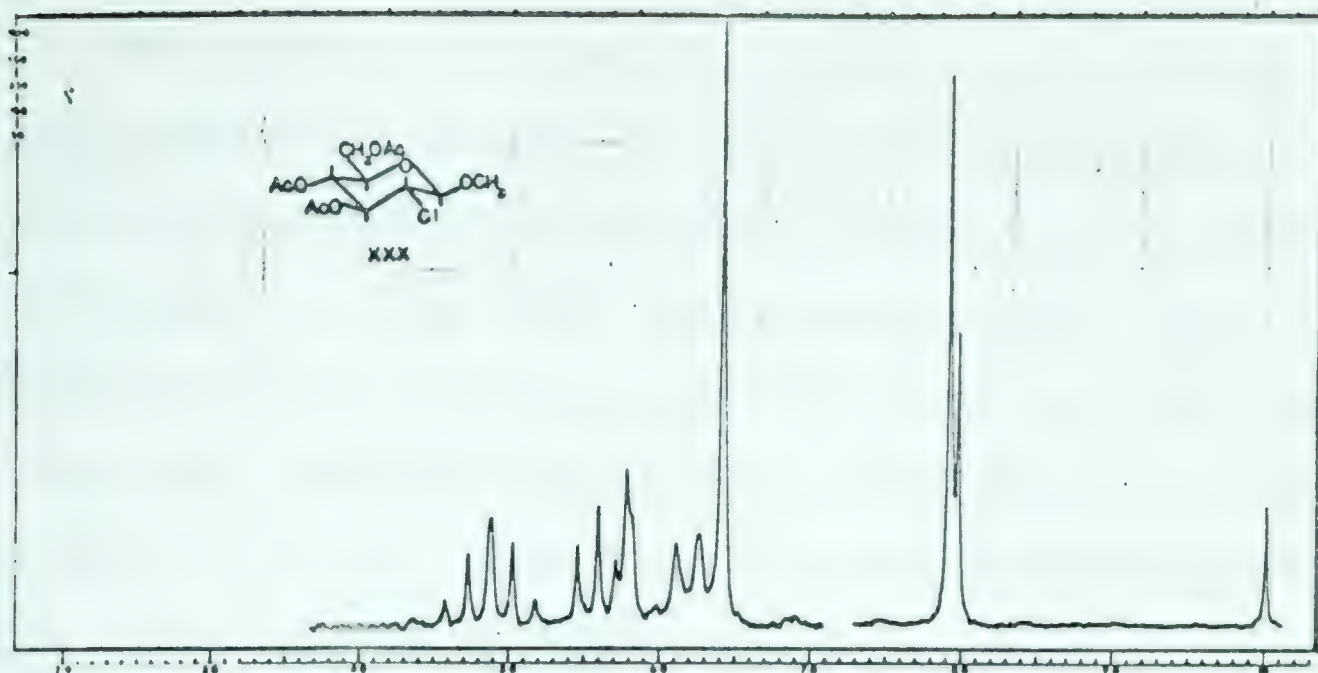


Fig. 7a Methyl 2-Chloro-2-deoxy-β-D-glucopyranoside Triacetate

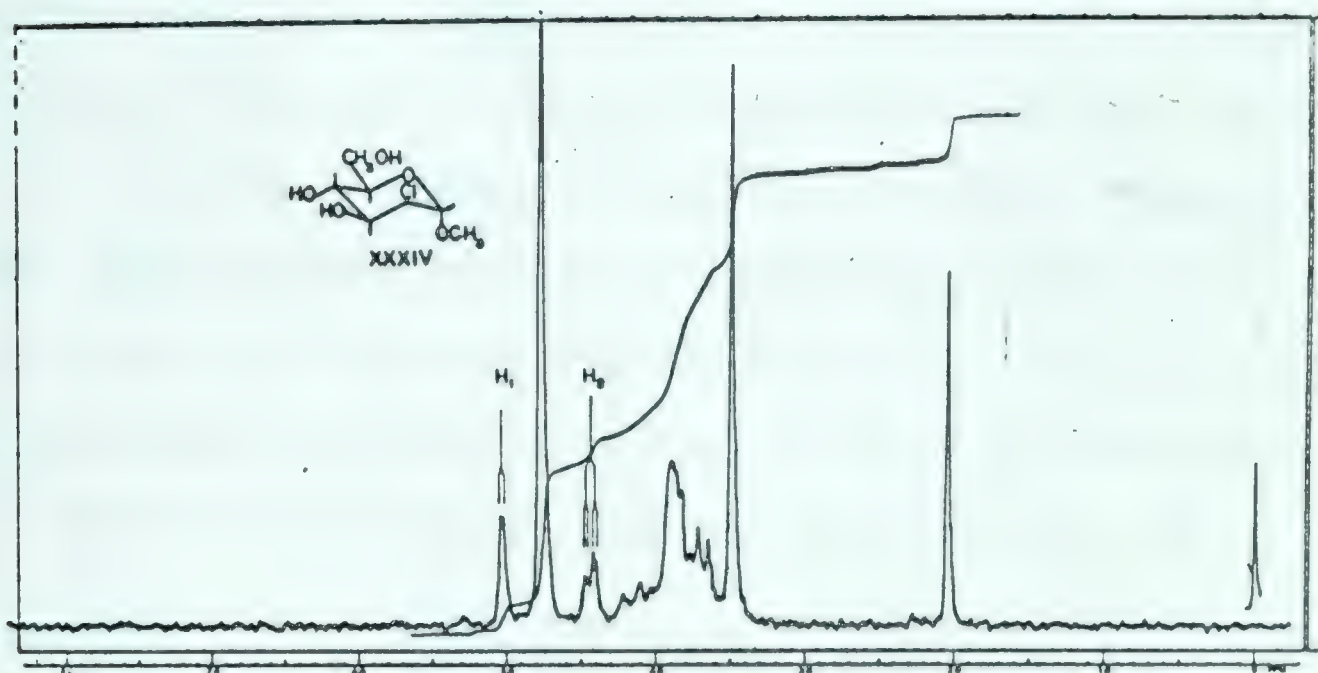


Fig. 7b Methyl 2-Chloro-2-deoxy-α-D-mannopyranoside

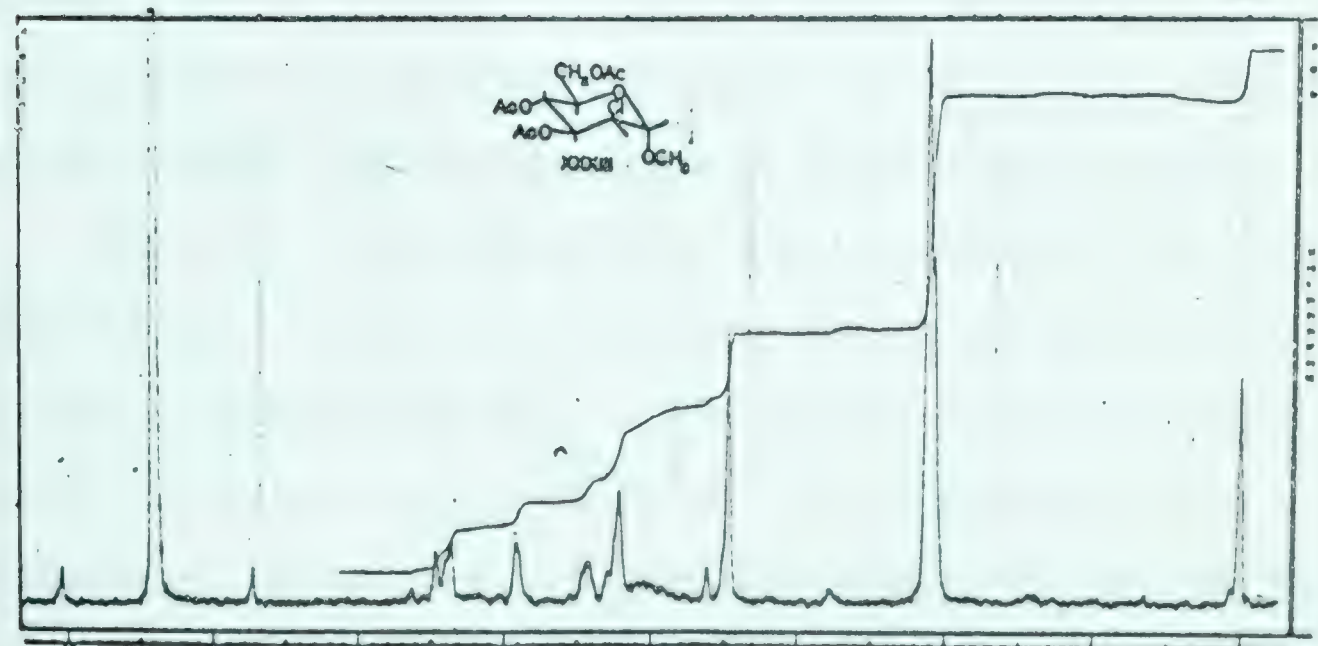


Fig. 7c Methyl 2-Chloro-2-deoxy-α-D-mannopyranoside Triacetate



$\alpha$ -D-glucopyranoside triacetate. It resisted crystallization.

The residue from the crystallization of XXX was deacetylated with methanolic ammonia to give a syrupy product, 2.26 g of which was fractionated on a cellulose column using *n*-butanol saturated with water. The first fraction contained 1.30 g of a substance with  $R_f$  0.87 (the  $R_f$  value for XXXI was 0.76) and its n.m.r. spectrum, measured in deuterium oxide (Fig. 7b) had a doublet with 1.2 c.p.s. spacing at 4.96 tau assigned to the anomeric hydrogen, and a quartet at 5.56 tau with spacings of 1.2 and 3.5 c.p.s. assigned to the 2-hydrogen of methyl 2-chloro-2-deoxy- $\alpha$ -D-mannopyranoside. The position of the signal for the methoxy group was at 6.50 tau. Its tri-O-acetyl derivative, XXXIII, (Fig. 7c) produced a signal at 6.55 tau for the methoxy group. Although the substance appeared virtually pure,  $[\alpha]_D$  45.2 (c, 1.7 in chloroform), it resisted crystallization. The n.m.r. spectrum of the triacetate is similar to that for the 2-bromo analogue XXVIII, described in Section C-II and shown in Fig. 4c.

## V. "Direct" Iodomethoxylation

1. Methyl 2-Deoxy-2-iodo- $\beta$ -D-glucopyranoside (XXXVIII) the Triacetate (XXXVI) of XXXVIII, Methyl 2-Deoxy-2-iodo- $\alpha$ -D-mannopyranoside (XXXIX) and the Triacetate (XXXVIII) of XXXIX

The n.m.r. spectrum (Fig. 5c) of the product of iodomethoxylation had signals for methoxy groups at 6.42 and 6.57 tau with relative intensities 3:5. The material was deacetylated by solution in a mixture of 45 ml water, 50 ml methanol and 5 ml of triethylamine. After 5 hours the solvents were removed by evaporation under reduced pressure and the residue was dissolved in



methanol and decolorized using charcoal. The charcoal was removed by filtration and the methanol by evaporation under reduced pressure, and the residue was dissolved with heating in 30 ml of ethanol. Within one hour, 2.01 g (36%) of the glucoside, XXXVII, crystallized. After two recrystallizations from ethanol, the compound had the physical constants: m.p. 187-188°,  $[\alpha]_D$  3.8° ( $c$ , 3.9 in water). The reported values (57) for methyl 2-deoxy-2-iodo- $\beta$ -D-glucopyranoside, XXXVII, are 189-189.5° and 6.9°, respectively. Acetylation in the usual manner using acetic anhydride and pyridine provided methyl 2-deoxy-2-iodo- $\beta$ -D-glucopyranoside triacetate, XXXVI; m.p. 94-95°,  $[\alpha]_D$  61.1° ( $c$ , 2.03 in chloroform). The n.m.r. spectrum of this compound is shown in Fig. 8a, and the resemblance to those of the 2-bromo (XXV) and 2-chloro (XXX) analogues (Figs. 4a and 7a, respectively), supported the assignment of structure. Hydrogenolysis (cf. section C-I) gave methyl 2-deoxy- $\beta$ -D-glucopyranoside.

The mother liquor from the above described glucoside was concentrated to a syrup in vacuo and dissolved in ethyl acetate, 20 ml. Nucleation with an authentic sample (57) then afforded 1.15 g (20%) of crystalline XXXIX contaminated (about 15%) with the glucoside. The product was extracted twice with 15 ml of cold ethanol, and the combined extracts (which were shown by n.m.r. to be free from the glucoside) on evaporation and crystallization from ethyl acetate gave 0.95 g of the pure mannoside, m.p. 147-8°,  $[\alpha]_D$  48.8° ( $c$ , 1.0 in water). The reported values (57) are 145-6° and 49.6°, respectively.

A further 1.05 g of mannoside was obtained when the mother liquor from the first crop of crystals was (i) clarified



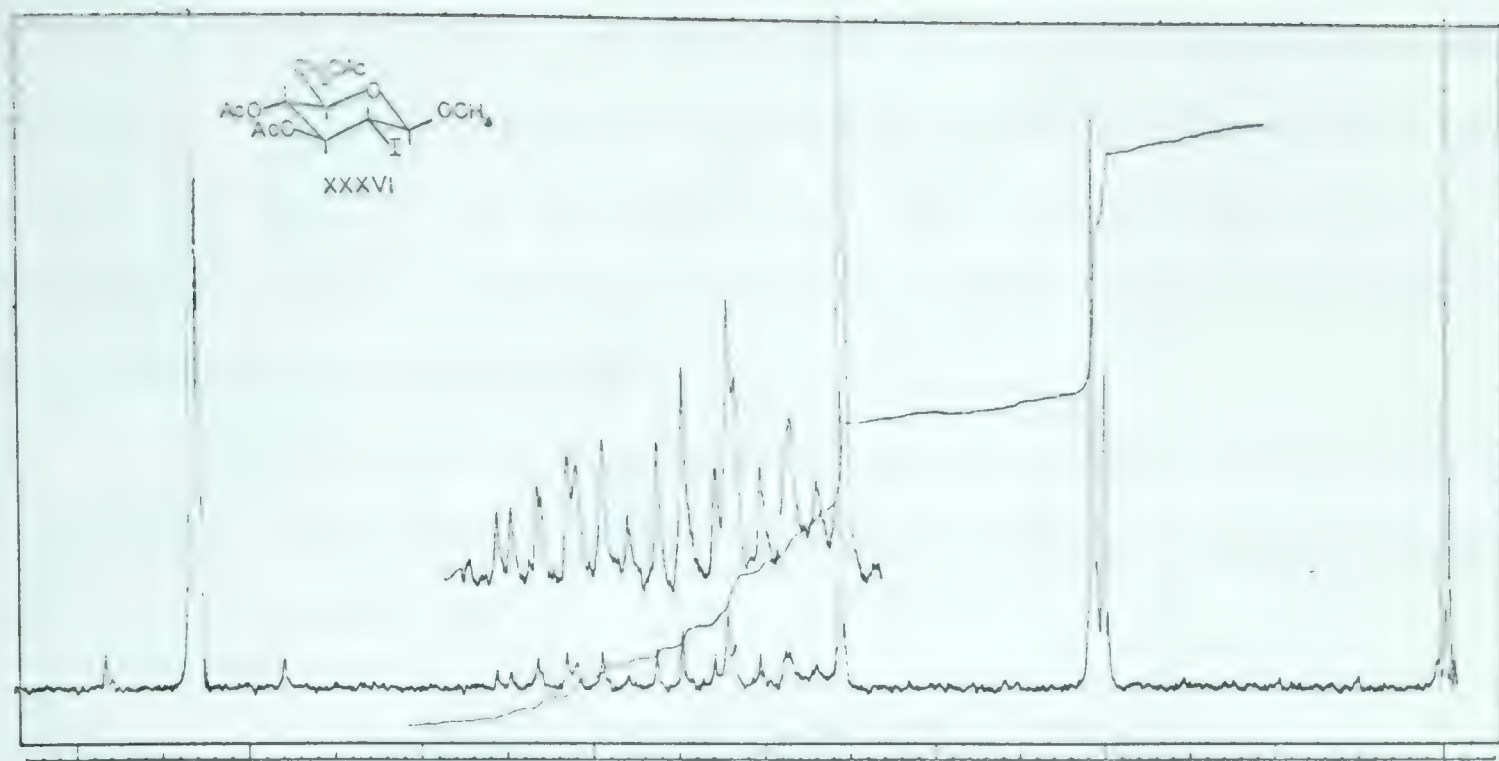


Fig. 8a Methyl 2-Deoxy-2-iodo-β-D-glucopyranoside Triacetate

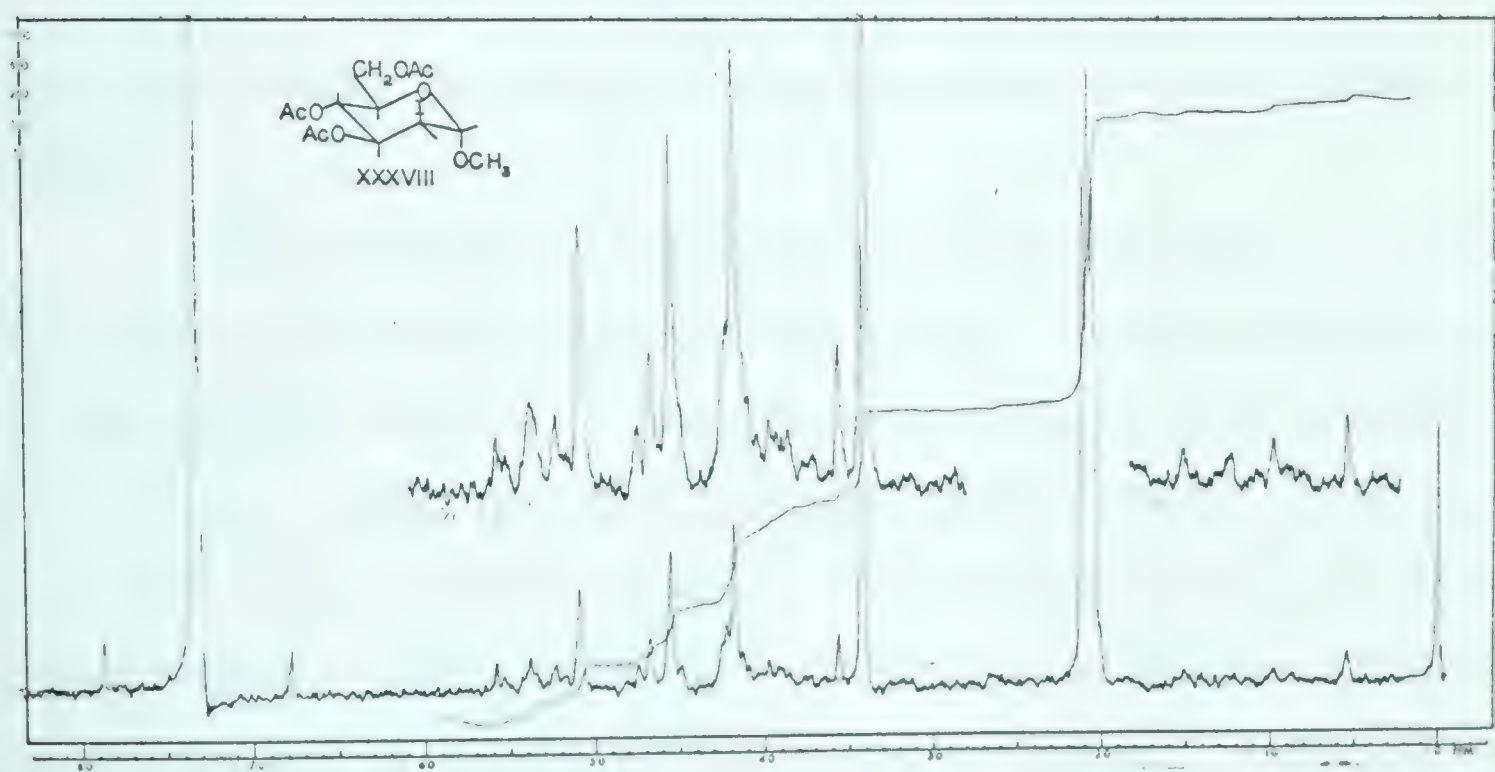


Fig. 8b Methyl 2-Deoxy-2-iodo-α-D-mannopyranoside Triacetate

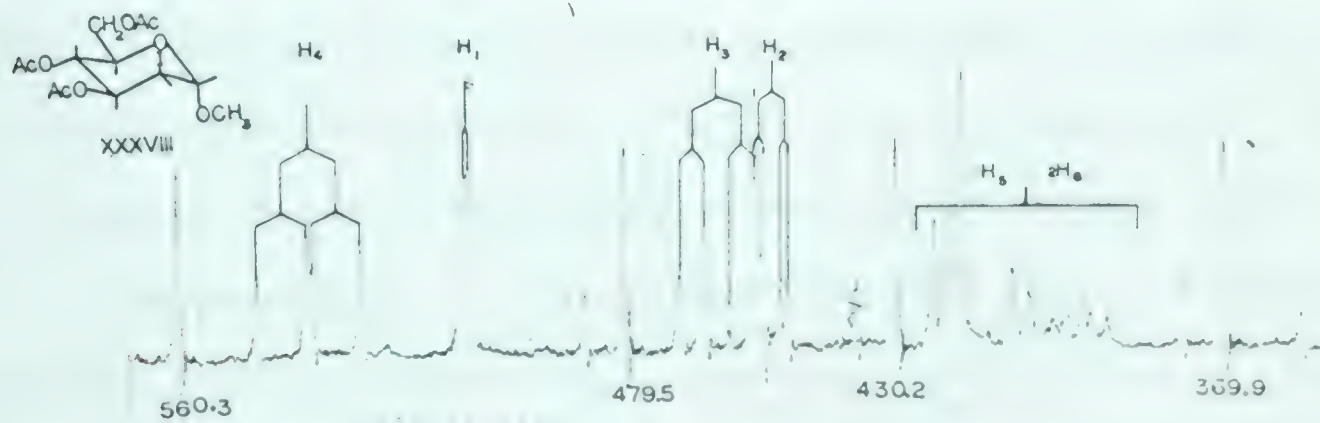


Fig. 8c Methyl 2-Deoxy-2-iodo-α-D-mannopyranoside Triacetate (100 Mc.p.s.)



with charcoal in boiling methanol, (ii) eluted through a short column of silicic acid and (iii) set to crystallize from ethyl acetate. Acetylation now afforded the syrupy triacetate, XXXVIII,  $[\alpha]_D 46.1^\circ$  (c, 1.5 in chloroform). The n.m.r. spectrum of this compound is shown in Figs. 8a and 8b and an anomaly connected with it is discussed on page 88.

Catalytic hydrogenolysis (see section C-I) of 450 mg of XXXVIII gave 118 mg (57%) of methyl 2-deoxy- $\alpha$ -D-glucopyranoside, XXXV, m.p. 90-91 $^\circ$  (57%).

#### D. Reactions of D-Galactal Triacetate

##### I. "Indirect" Bromomethoxylation

1. 2-Bromo-2-deoxy-3,4,6-tri-O-acetyl- $\alpha$ -D-galactopyranosyl Bromide (XLI) and 2-Bromo-2-deoxy-3,4,6-tri-O-acetyl- $\alpha$ -D-talopyranosyl Bromide (XLII).

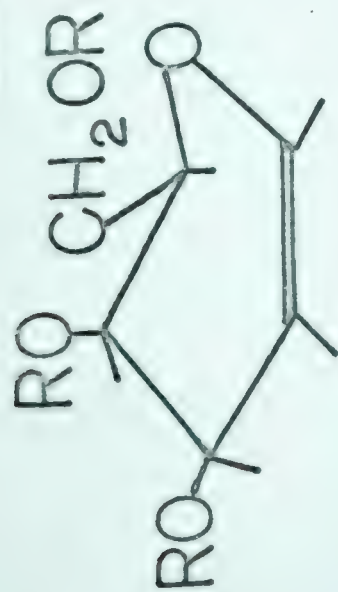
Bromination of D-galactal triacetate gave a 1:1 mixture of two components which comprised 88% (n.m.r. estimation; cf section C-I) of the syrupy material. The anomeric signals were doublets at 3.20 and 3.46 tau (Fig. 2b) with coupling constants ( $J_{12}$ ) of less than 1 and 4.0 c.p.s., respectively. By comparison with the dibromides from triacetyl glucal (Fig. 2a), these compounds were assigned as 2-bromo-2-deoxy-3,4,6-tri-O-acetyl- $\alpha$ -D-talo- and  $\alpha$ -D-galacto-pyranosyl bromides, XLI and XLII, respectively.

2. Methyl 2-Bromo-2-deoxy- $\alpha$ -D-talopyranoside Triacetate (XLIII), Methyl 2-Bromo-2-deoxy- $\beta$ -D-galactopyranoside Triacetate (XLV) and Methyl 2-Bromo-2-deoxy- $\beta$ -D-talopyranoside Triacetate (XLVI).

Methanolysis of the dibromides XLI and XLII (see section B-I) gave a product whose n.m.r. spectrum at 60 Mc.p.s. showed signals for only two glycosidic methoxyl groups at 6.42 (XLV) and 6.58 (XLIII) tau, but higher resolution (HR 100) showed a third component



Reaction Products from D - Galactal Triacetate

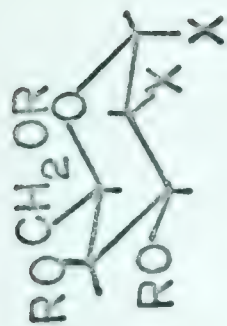


XL

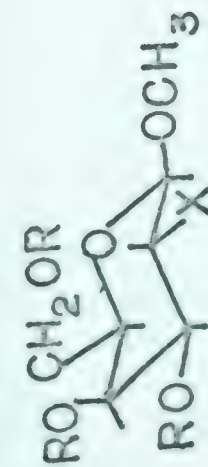


XLI X = Br

XLIX X = Cl



XLII X = Br



XLIV R = Ac; X = Br

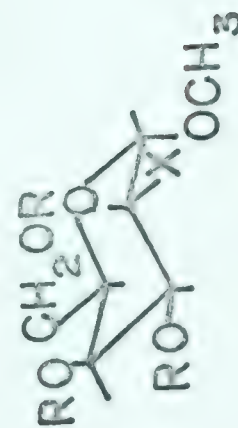
XLVII R = X = H

L R = Ac; X = Cl

LI R = H; X = Cl

IV R = Ac; X = I

VII R = H; X = I

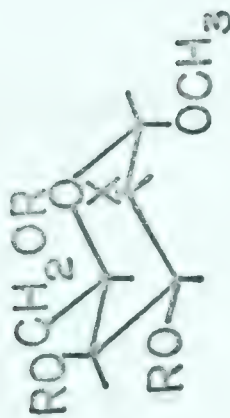


XLIV R = X = H

XLVIII R = Ac; X = Br

LI R = Ac; X = Cl

LIV R = H; X = Cl

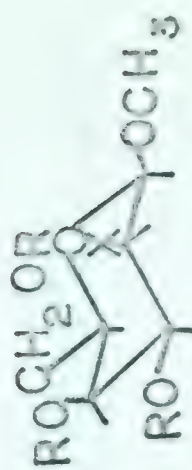


XLIII R = Ac X = Br

LI R = Ac, X = Cl

LVI R = Ac X = I

LVII R = H X = I



XLVI R = Ac; X = Br



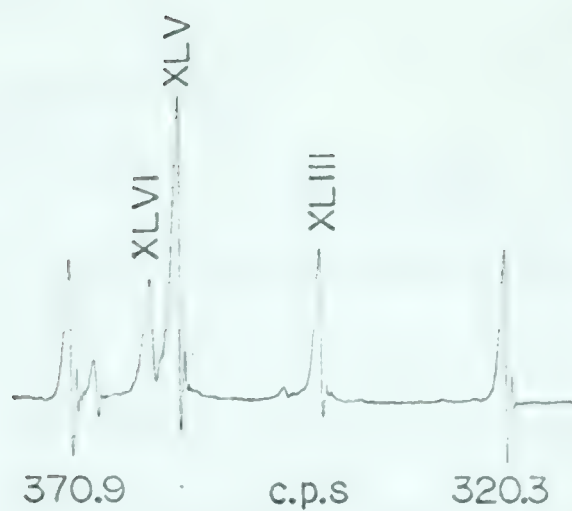


Fig. 9a Products from "Indirect" Bromomethoxylation of D-Galactal Triacetate

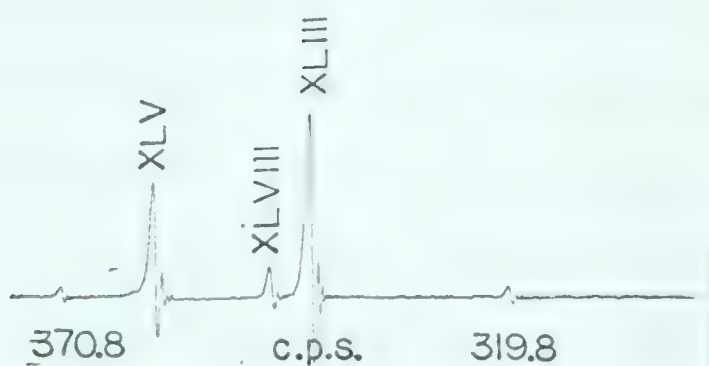


Fig. 9b Products from "Direct" Bromomethoxylation of D-Galactal Triacetate

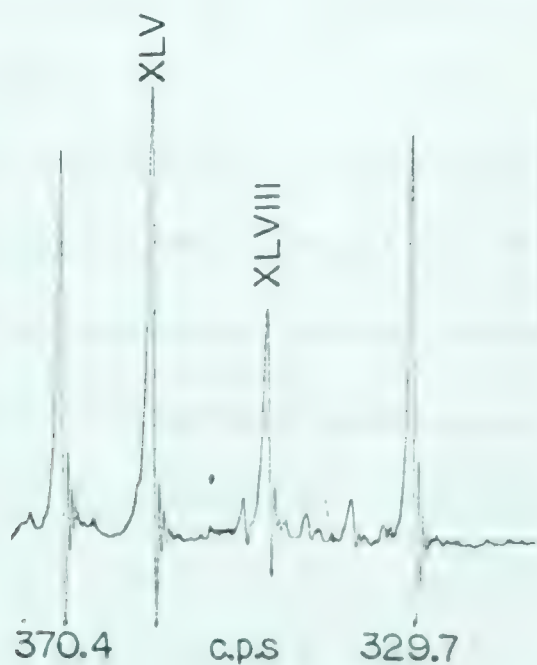


Fig. 9c Anomerization of Methyl 2-Bromo-2-deoxy- $\beta$ -D-galactopyranoside Triacetate



at slightly lower field, 6.39 tau (XLVI). The percentages of XLV, XLIII and XLVI as determined by n.m.r. at 100 Mc.p.s. (Fig. 9a), were 50, 27 and 23 respectively.

A portion (3.0 g) of the mixture was applied to six sheets of Whatman 3MM paper impregnated with dimethyl sulphoxide (152) and eluted with Skellysolve B for seven hours. After drying, strips were cut from the sides and centre of the sheets and developed with the silver nitrate-sodium hydroxide spray (150), and, although there was considerable overlapping, a zone was isolated which was extracted with chloroform. Dimethyl sulphoxide was removed by washing with water, and by eluting the chloroform solution through a column of silicic acid. Evaporation then provided 330 mg of material with a specific rotation of  $65.6^{\circ}$  ( $c$ , 1.8 in chloroform) which failed to crystallize. Its n.m.r. spectrum in pyridine (Fig. 10a) shows the signal for the anomeric hydrogen at 4.70 tau with a spacing (1.5 c.p.s.) characteristic (128) for hydrogens in equatorial-equatorial relationship. The chemical shift for the methoxy group (67) gives added support for the structure of methyl 2-bromo-2-deoxy- $\alpha$ -D-talopyranoside triacetate. Since its methoxy resonance occurs at 6.58 tau, this compound, XLIII, was that produced in 27 per cent yield.

Hydrogenolysis of XLIII in the usual manner (section C-I) gave methyl 2-deoxy- $\alpha$ -D-galactopyranoside, XLIV, (section D-VI).

The other two components were not resolved, but the material recovered from the chromatogram (1.6 g), on standing in ethanol yielded 0.62 g of a substance which after two recrystallizations from ethanol had the physical constants m.p.  $134-135^{\circ}$ ,  $[\alpha]_D$   $33.2^{\circ}$  ( $c$ , 1.37 in chloroform). Calc. for  $C_{13}H_{19}O_8Br$ : C, 40.73;



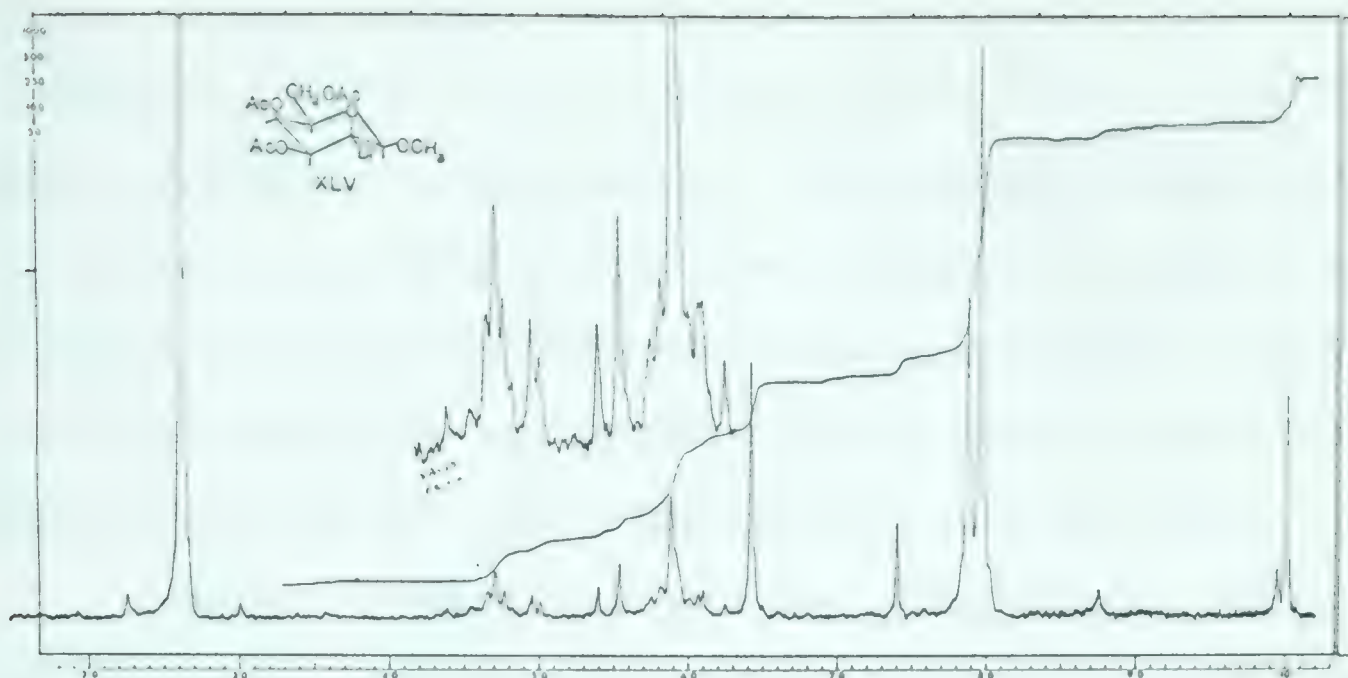


Fig. 10a Methyl 2-Bromo-2-deoxy- $\beta$ -D-galactopyranoside Triacetate

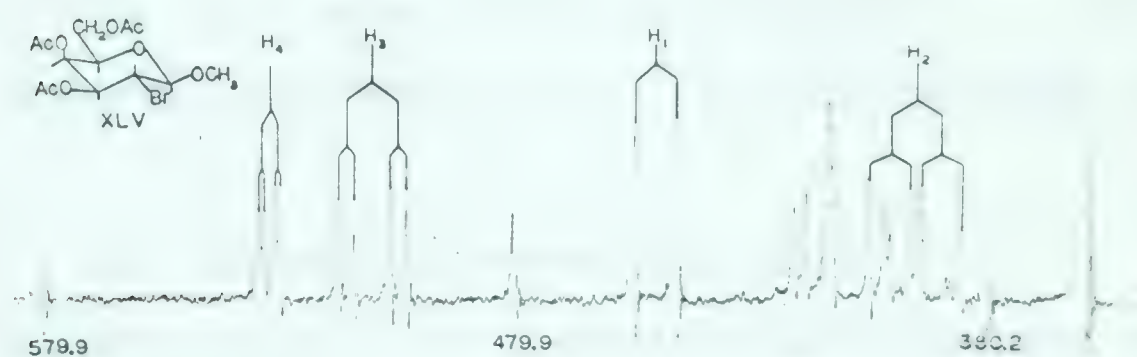


Fig. 10b Methyl 2-Bromo-2-deoxy- $\beta$ -D-galactopyranoside Triacetate (100 Mc.p.s.)

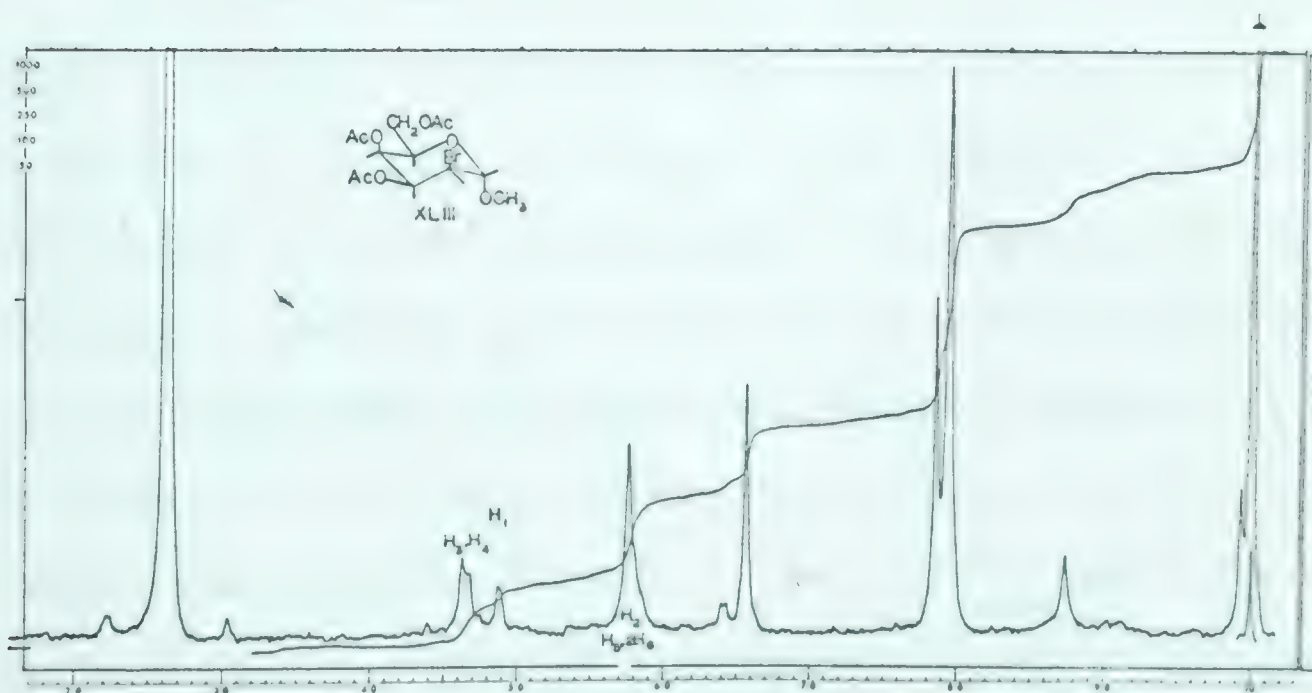


Fig. 10c Methyl 2-Bromo-2-deoxy- $\alpha$ -D-talopyranoside Triacetate



H, 4.97%. Found: C, 40.98; H, 4.88%. Its n.m.r. spectrum at 100 Mc.p.s. (Fig. 10b) was completely first order, and the assignment of the 1-, 2-, 3- and 4-hydrogens shown were made on the basis of double irradiation experiments. The coupling constants  $J_{12} = 8.5$  c.p.s. and  $J_{23} = 10.3$  c.p.s. are obviously consistent with the structure of methyl 2-bromo-2-deoxy- $\beta$ -D-galactopyranoside triacetate and the similarity with the spectra of the 2-chloro and 2-iodo analogues (Fig. 12a and 13a respectively) will be noted.

A second crystalline specimen could not be obtained from the acetylated or deacetylated mother liquor, but since hydrogenolysis of a portion of this mixture (section C-1) yielded methyl 2-deoxy- $\beta$ -D-galactopyranoside, XLVII (section D-VI) as the only sugar, the third glycoside must also have the  $\beta$ -D-configuration. Consequently the compound is methyl 2-bromo-2-deoxy- $\beta$ -D-talopyranoside triacetate, XLVI.

## II. "Direct" Bromomethoxylation

1. Methyl 2-Bromo-2-deoxy- $\alpha$ -D-talopyranoside Triacetate (XLIII), Methyl 2-Bromo-2-deoxy- $\beta$ -D-galactopyranoside Triacetate (XLV), and Methyl 2-Bromo-2-deoxy- $\alpha$ -D-galactopyranoside Triacetate (XLVII).

The syrupy reaction product from bromomethoxylation of D-galactal triacetate contained three components whose methoxyl signals in the n.m.r. at 100 Mc.p.s. (Fig. 9b) were at 6.41, 6.54 and 6.58 tau in 37, 11 and 52 per cent relative amounts respectively. The A-60 n.m.r. spectrum of the mixture in pyridine is shown in Fig. 11a. In one experiment, the original reaction product, 1.4 g (3.7 mM) was dissolved in 25 ml methanol containing silver acetate (1.67 g, 10 mM) and bromine (1.60 g, 10 mM). The mixture was allowed to stand with stirring for 24 hours after which isolation in the usual manner



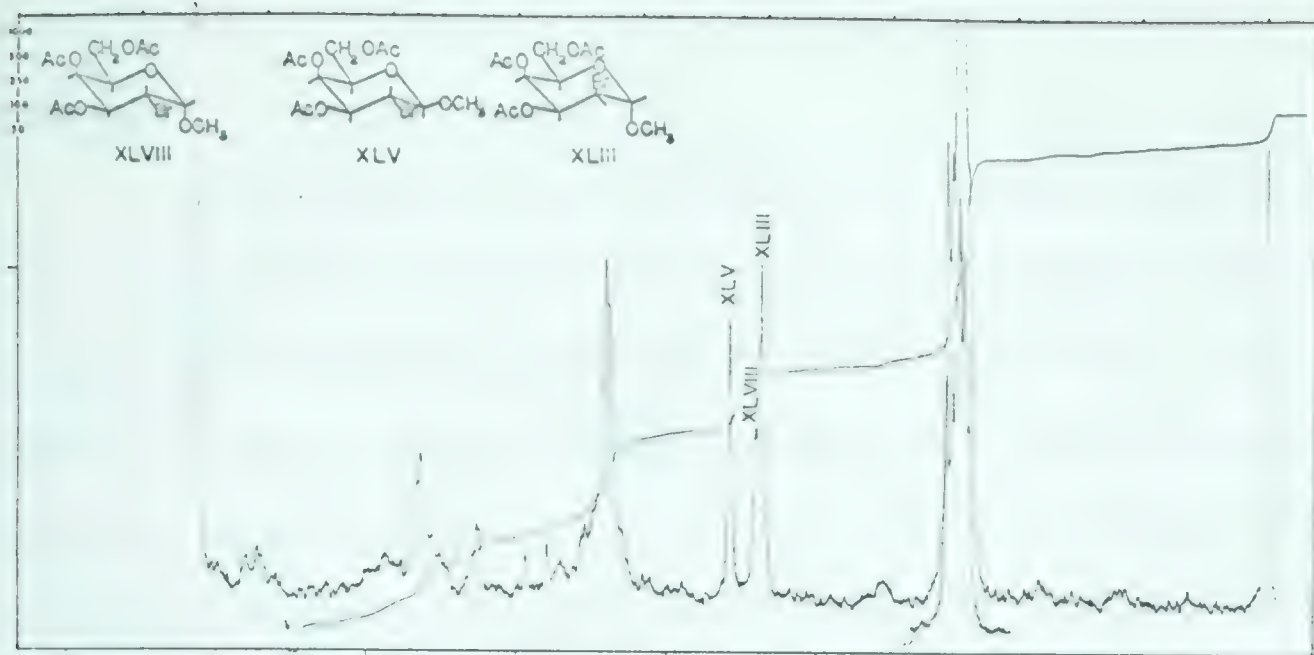


Fig. 11a Products from "Direct" Bromomethoxylation of D-Galactal Triacetate

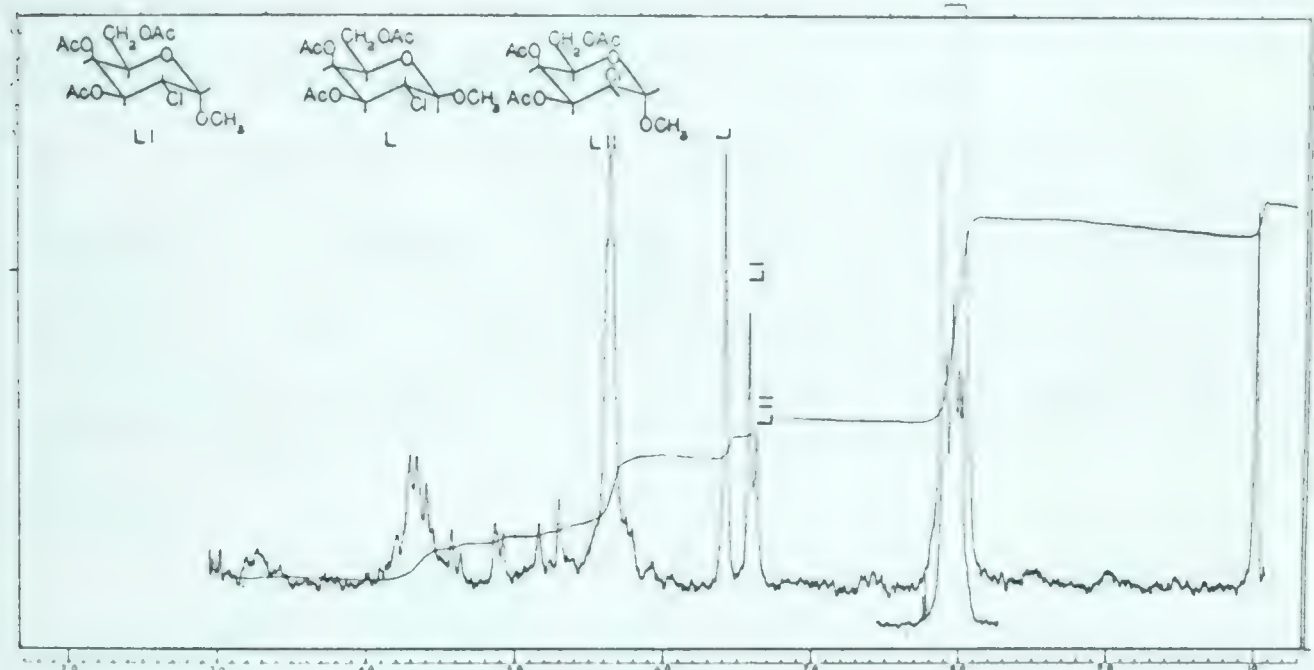


Fig. 11b Products from "Direct" Chloromethoxylation of D-Galactal Triacetate

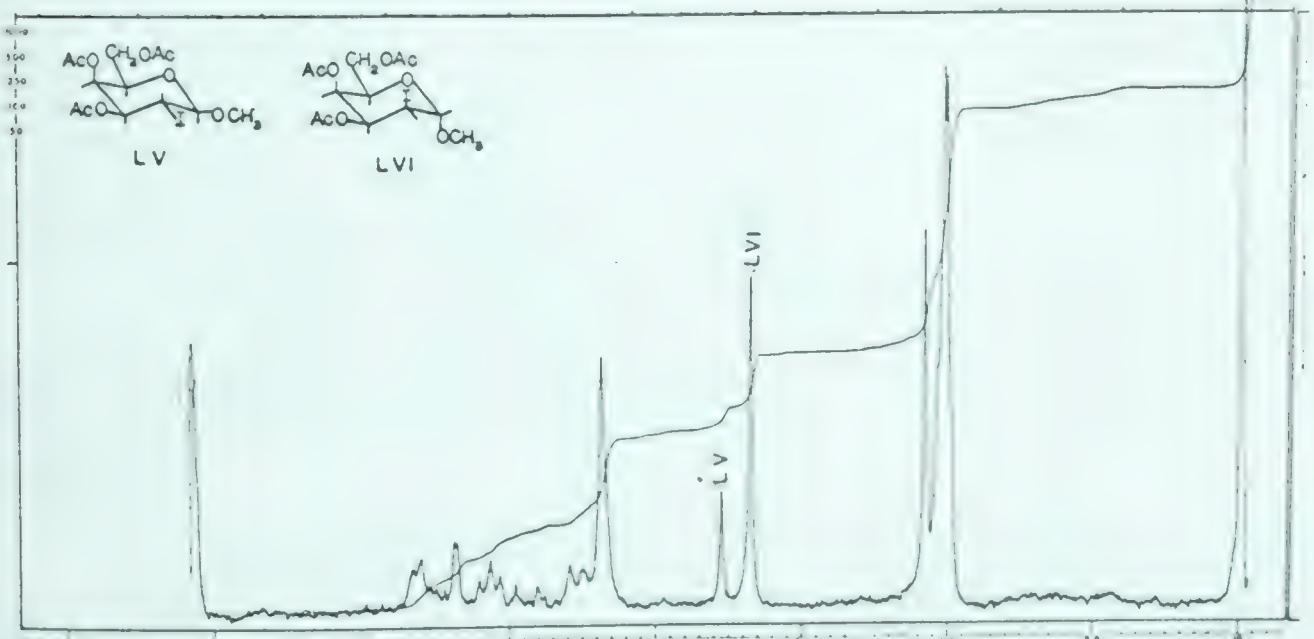


Fig. 11c Products from "Direct" Iodomethoxylation of D-Galactal Triacetate



afforded the starting material in an identical composition. The reaction medium therefore did not promote equilibration of the components.

A portion of the reaction product was deacetylated with 25 ml of 5% triethylamine in 50% aqueous methanol and paper chromatography showed three spots of  $R_f$  0.63, 0.83 and 0.89. This material (1.89 g) was chromatographed on a cellulose column with n-butanol as irrigant. The 490 to 690 ml fraction yielded non-crystalline material which was purified by acetylation with acetic anhydride in pyridine. The syrupy triacetate, 1.06 g, was identical to the above described methyl 2-bromo-2-deoxy- $\alpha$ -D-talopyranoside triacetate, XLIII (section D-I 2.).

The 885 to 1800 ml fraction from the cellulose chromatogram contained the component of  $R_f$  0.63 and upon acetylation, 0.445 g of the previously described (section D-I 2) methyl 2-bromo-2-deoxy- $\beta$ -D-galactopyranoside, XLV, crystallized from a cooled solution in ethanol.

The component of  $R_f$  0.83 was not obtained in a pure state, but the 690 to 870 ml fraction of the chromatogram yielded material which on acetylation gave 0.168 g of a mixture of XLVIII and the above described  $\alpha$ -D-taloside, XLIII. The former gave its methoxyl signal at 6.54 tau and was evidently the minor component of the "direct" bromomethoxylation (Fig. 9b).

Hydrogenolysis of this mixture as in Section B-I gave methyl 2-deoxy- $\alpha$ -D-galactoside, XLIV (section D-VI), as the only product.

Titanium tetrachloride isomerisation (cf section C2) of the  $\beta$ -D-galactopyranoside, XLV, achieved partial anomerisation (40%)



to the  $\alpha$ -D-isomer (Fig. 9c) which gave its methoxyl resonance at 6.54 tau. The minor component in the "direct" reaction is therefore methyl 2-bromo-2-deoxy- $\alpha$ -D-galactopyranoside triacetate, XLVIII.

### III. "Indirect" Chloromethoxylation

#### 1. 2-Chloro-2-deoxy-3,4,6-tri-O-acetyl- $\alpha$ -D-galactopyranosyl Chloride (XLIX)

Chlorination of D-galactal triacetate gave a product in 96% yield which showed in the n.m.r. (Fig. 6b) only one signal at low field, 3.77 tau, whose coupling constant of 4.0 c.p.s. required it to arise from 2-chloro-2-deoxy-3,4,6-tri-O-acetyl- $\alpha$ -D-galactopyranosyl chloride, XLIX. The substance, which failed to crystallize, had a specific rotation of  $71.5^\circ$  ( $c$ , 3.57 in chloroform).

#### 2. Methyl 2-Chloro-2-deoxy- $\alpha$ -D-galactopyranoside triacetate, L.

The product of methanolysis of XLIX contained a single crystalline glycoside which was identical to that discussed immediately below.

### IV. "Direct" Chloromethoxylation

#### 1. Methyl 2-Chloro-2-deoxy- $\beta$ -D-galactopyranoside (LIII) and the Triacetate (L) of LIII, Methyl 2-Chloro-2-deoxy- $\alpha$ -D-galactopyranoside (LIV) and the Triacetate (LI) of LIV, and Methyl 2-Chloro-2-deoxy- $\alpha$ -D-talopyranoside Triacetate (LIII).

The n.m.r. spectrum (Fig. 11b) of the syrupy product in pyridine indicated the presence of three methyl glycosides, L, LI and LII, at 6.42, 6.58 and 6.62 tau in 53, 39 and 8 per cent relative amounts, respectively. On standing overnight in ethanol, 1.75 g (14%) of the major component separated, which, after two recrystallizations from ethanol, melted at  $127-9^\circ$ ,  $[\alpha]_D$   $33.3^\circ$  ( $c$ , 1.5 in chloroform).





Fig. 12a Methyl 2-Chloro-2-deoxy- $\beta$ -D-galactopyranoside Triacetate

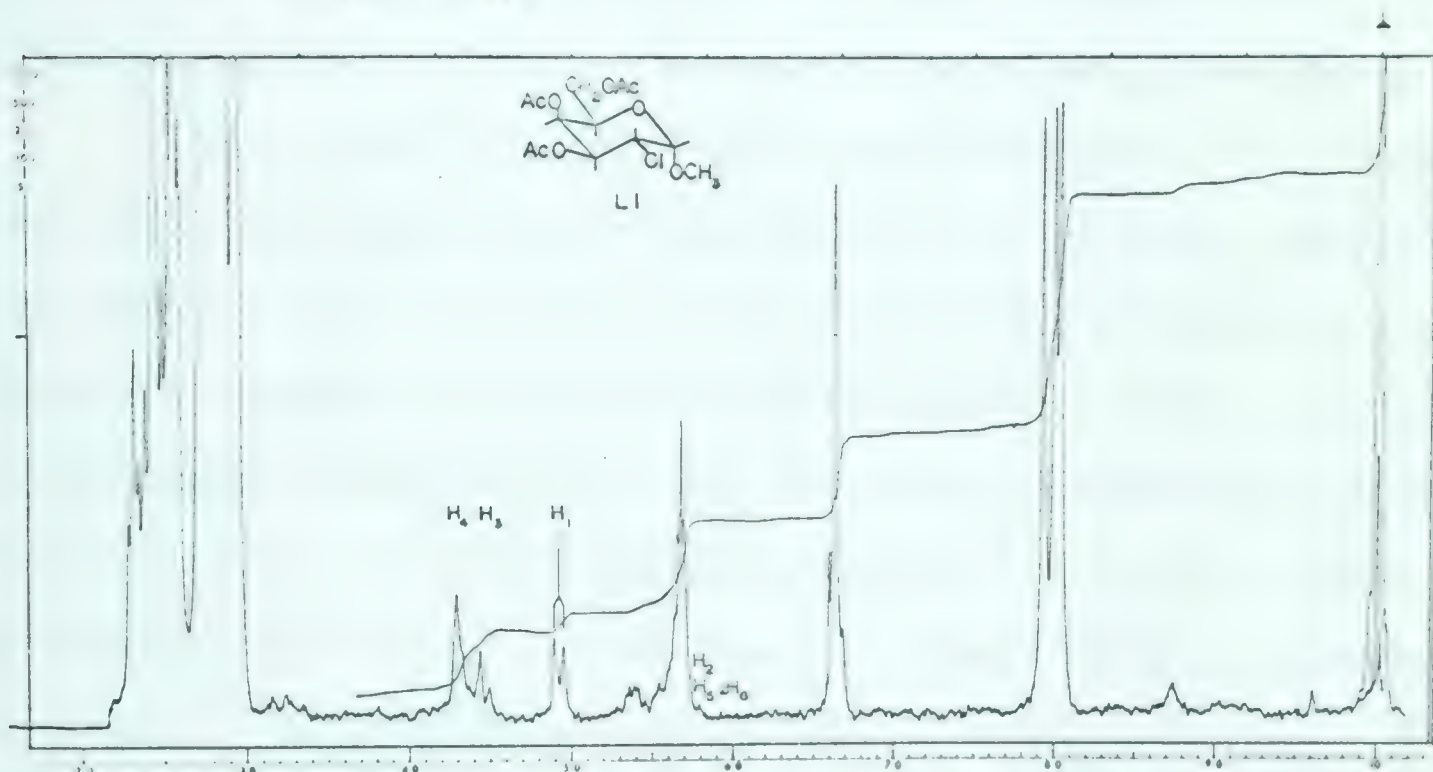


Fig. 12b Methyl 2-Chloro-2-deoxy- $\alpha$ -D-galactopyranoside Triacetate

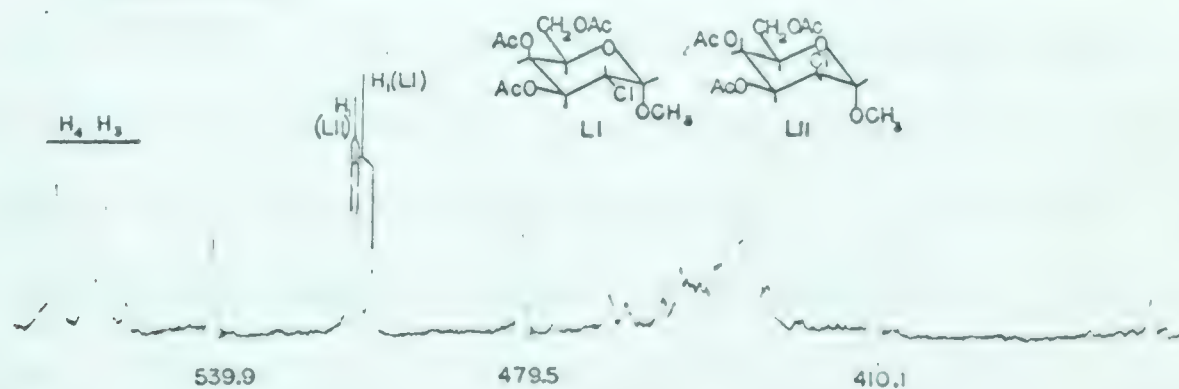


Fig. 12c Mixture of Methyl 2-Chloro-2-deoxy- $\alpha$ -D-galacto and - $\alpha$ -D-talo-pyranoside Triacetates (100 Mc.p.s.)



Calc. for  $C_{13}H_{19}O_8Cl$ : C, 46.15; H, 5.62%. Found: C, 46.02; H, 5.38%. The favourable comparison (see Table I) of its n.m.r. spectrum (Fig. 12a) with that of the 2-bromo derivative, XIV, reported in Fig. 10, indicates that the compound is methyl 2-chloro-2-deoxy- $\beta$ -D-galactopyranoside triacetate, L. Treatment of the latter with 5% triethylamine in 50% aqueous methanol for two hours afforded the deacetylated sugar, LIII, m.p. 143.5-144.5°,  $[\alpha]_D$  11.0° (c, 1.06 in methanol).

Treatment of L with titanium tetrachloride (section C-IV) in chloroform resulted in its partial anomerisation to give 37% of a glycoside whose methoxyl signal occurred at 6.58 tau and was evidently the component produced in second highest yield. LI is, therefore, methyl 2-chloro-2-deoxy- $\alpha$ -D-galactopyranoside triacetate.

The mother liquor from crystallization of L was deacetylated with 5% triethylamine in 50% aqueous methanol, but fractionation was not achieved on a cellulose column, neither were the components resolved on paper chromatography. Hence, preparative reverse phase chromatography, as described in section D-I was attempted on the original reaction product. By this means there was obtained 638 mg of material which proved to be a mixture of LI and LII. On refrigeration of the solution in ether: Skellysolve B (1:1) for several months, partial crystallization of LI occurred; m.p. 86-88°,  $[\alpha]_D$  73.8° (c, 1.46 in chloroform). Deacetylation of LI led to methyl 2-chloro-2-deoxy- $\alpha$ -D-galactopyranoside, LIII, as a crystalline specimen, m.p. 145-7°,  $[\alpha]_D$  75.37° (c, 0.52 in methanol). The n.m.r. spectrum of this compound (LIII) is shown in Fig. 12b. By comparison with the  $\beta$ -D-anomer (Fig. 12) it is evident that the 3- and 5- hydrogens are deshielded by the C-1 methoxy group and are shifted downfield. A similar



deshielding effect of the axial methoxyl group in XIII (Fig. 10c) can be observed.

The mother liquor from the partial crystallization of LI was shown by n.m.r. examination (HR 100) Fig. 12c to be an equal mixture of the  $\alpha$ -D-galactoside, LI, and the  $\alpha$ -D-taloside, LII. The anomeric signals for both compounds were overlapping. That for the former, by comparison with the pure substance, Fig. 12b, gave a doublet of spacing 3.8 c.p.s. at 4.90 tau, and that for the latter (LII) was a doublet centred at 4.88 tau with a spacing of 1.1 c.p.s. LII was therefore methyl 2-chloro-2-deoxy- $\alpha$ -D-talopyranoside triacetate, and since the optical rotation of the mixture was  $67.8^\circ$  ( $c$ , 2.22 in chloroform), pure LII has a specific rotation of  $61.8^\circ$ .

#### V. "Direct" Iodomethoxylation

1. Methyl 2-Deoxy-2-iodo- $\beta$ -D-galactopyranoside (LVII) and the Triacetate (LV) of LVII, and Methyl 2-Deoxy-2-iodo- $\alpha$ -D-talopyranoside (LVIII) and the Triacetate (LVI) of LVIII

Iodomethoxylation of D-galactal triacetate (Fig. 11c) resulted in the formation in 19 and 81% relative amounts of two isomers, LV and LVI, which, in view of their vastly different rates of movement on dimethyl sulphoxide impregnated paper (section D-I) were readily separated on a preparative scale. The zones formed on fractionation of the reaction product (2.0 g) on four sheets of Whatman 3MM paper were detected by exposing the developed chromatograms to ultraviolet light. Extraction and purification of the slower moving zone afforded 0.209 g of LV which crystallized from ethanol. After two recrystallizations, m.p.  $125-6^\circ$   $[\alpha]_D$   $13.95^\circ$  ( $c$ , 4.08 in chloroform). Calc. for  $C_{13}H_{19}O_8I$ : C, 36.28;



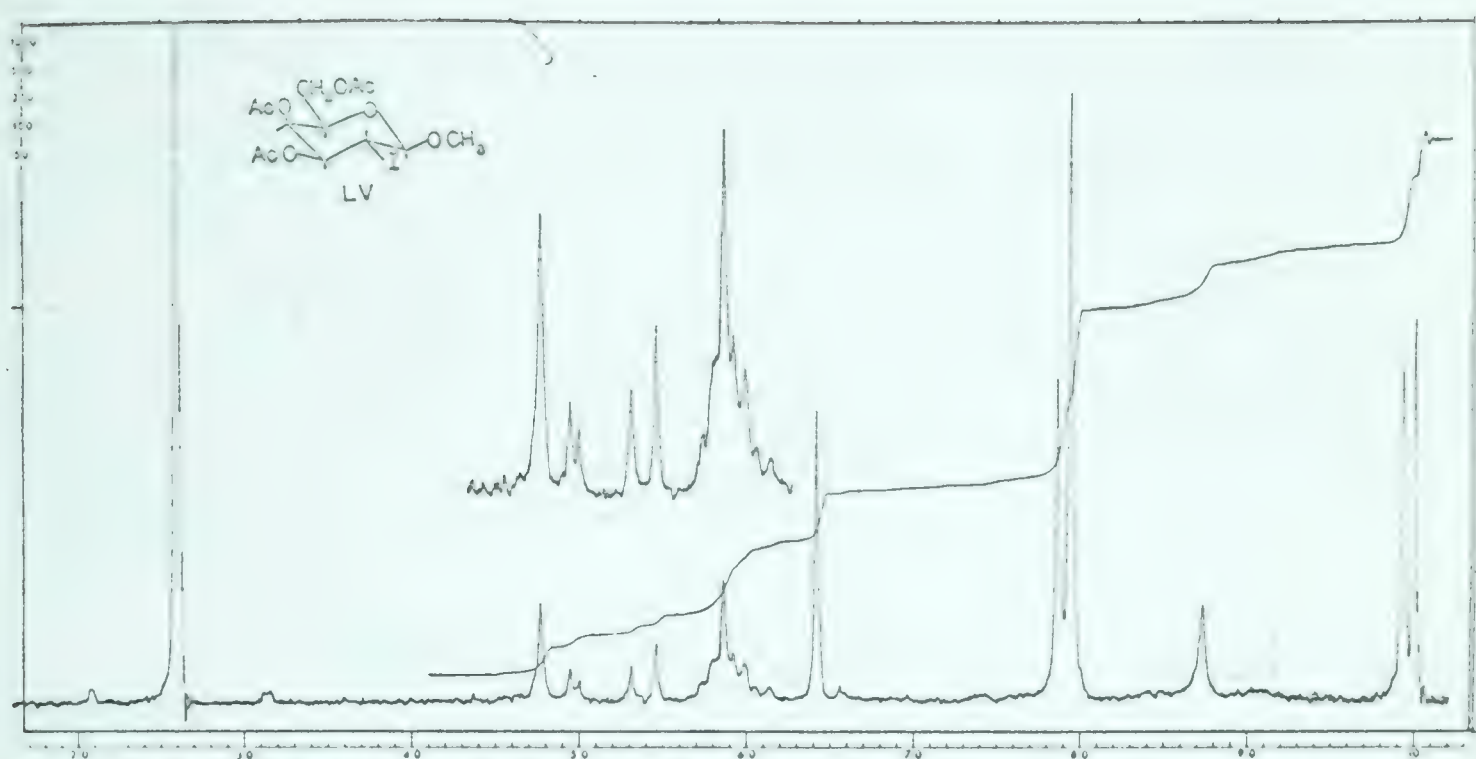


Fig. 13a Methyl 2-Deoxy-2-iodo- $\beta$ -D-galactopyranoside Triacetate

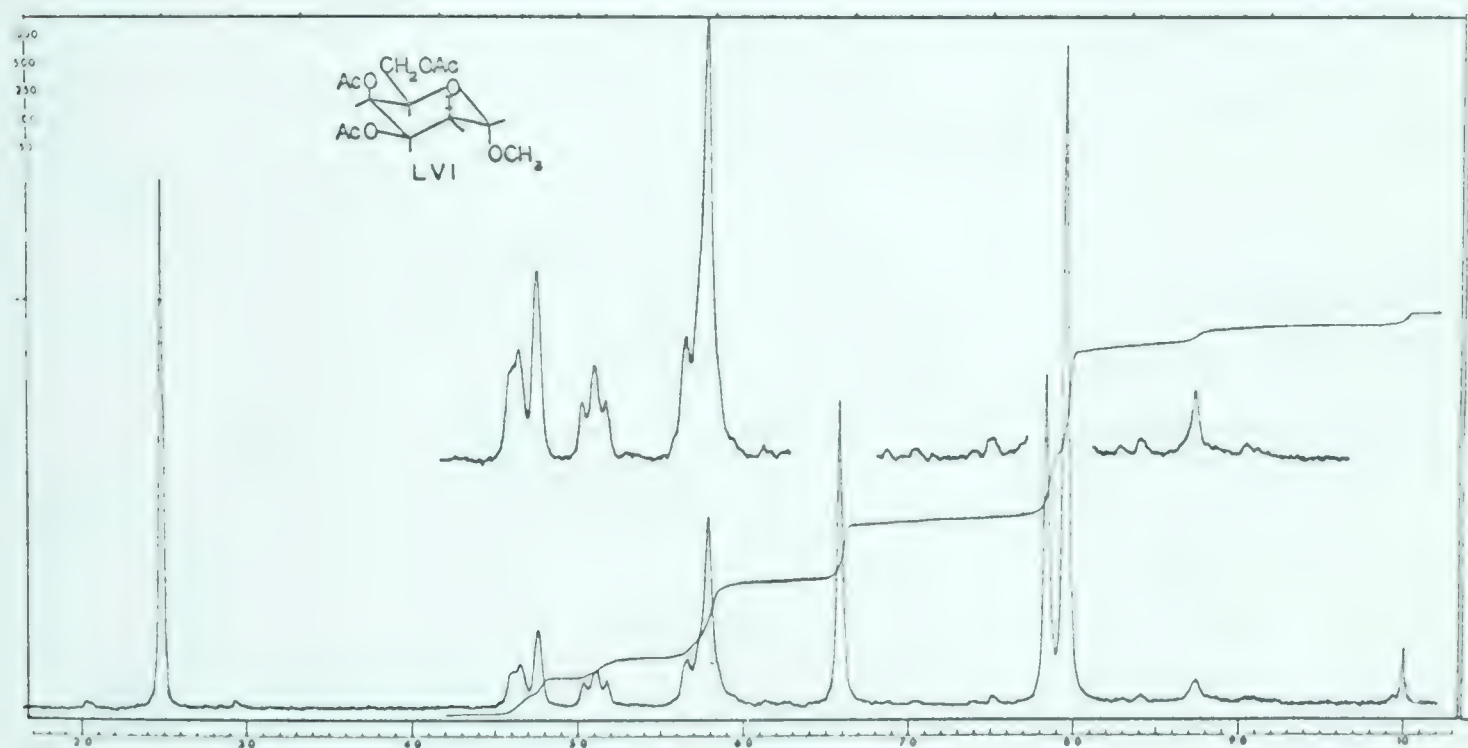


Fig. 13b Methyl 2-Deoxy-2-iodo- $\alpha$ -D-talopyranoside Triacetate

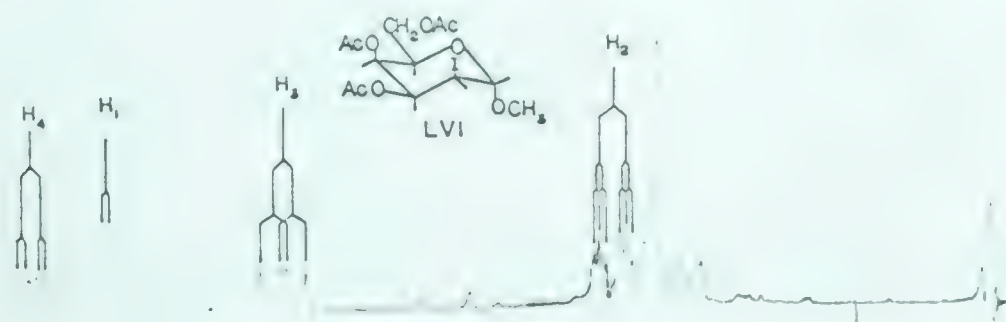


Fig. 13c Methyl 2-Deoxy-2-iodo- $\alpha$ -D-talopyranoside Triacetate (100 Mc.p.s.)



H, 4.42%. Found: C, 36.16; H, 4.54%. The n.m.r. spectrum of this compound is shown in Fig. 13a, and its characterization as methyl 2-deoxy-2-iodo- $\beta$ -D-galactopyranoside is evident by comparison with the 2-bromo (XLV) and 2-chloro (L) analogues, (Figs. 10a and 12a), respectively.

Deacetylation of LV (50 mg) with 10 ml of 5% triethylamine in 50% aqueous methanol gave 34 mg of non-crystalline methyl 2-deoxy-2-iodo- $\beta$ -D-galactopyranoside, LVII,  $[\alpha]_D 34.6^\circ$  ( $c$ , 0.47 in methanol).

Hydrogenolysis (cf section C-I) of 5 mg of LVII gave methyl 2-deoxy- $\beta$ -D-galactopyranoside, XLVII (see section D-VI).

The faster moving zone from the above described chromatogram gave 0.970 g of syrupy LVI,  $[\alpha]_D 27.7^\circ$  ( $c$ , 3.13 in chloroform). The n.m.r. spectrum of this compound is shown in Fig. 13b and is discussed on page 88.

Deacetylation of 70 mg gave the free sugar, LVIII, which was also non-crystalline,  $[\alpha]_D 57.0^\circ$  ( $c$ , 2.40 in methanol).

Hydrogenolysis (cf section C-I) of LVI gave methyl 2-deoxy- $\alpha$ -D-galactopyranoside, XLIV (see section D-VI).

## VI. Methanolysis

### 1. Methyl 2-Deoxy- $\alpha$ -D-galactopyranoside (XLIV) and Methyl 2-Deoxy- $\beta$ -D-galactopyranoside (XLVII)

A mixture of methyl 2-deoxy- $\alpha$ -D- and  $\beta$ -D-galactopyranosides obtained by treating D-galactal (1.66 g) with 10 ml of 3% methanolic hydrogen chloride for two hours (158) gave two spots on paper chromatograms,  $R_f$  0.39 and 0.46. The mixture (250 mg) was dissolved in 1.5 ml of freshly distilled benzaldehyde containing 0.46 g of powdered zinc chloride which had been previously



fused. The mixture was shaken for twelve hours and then poured into 15 ml ice water. A curdy precipitate formed, and on isolation, decolorization and crystallization from ethanol, there was obtained 70 mg (19%) of methyl 4,6-O-benzylidene-2-deoxy- $\alpha$ -D-galactopyranoside which after two recrystallizations from ethanol melted at 177-8°,  $[\alpha]_D$  122° ( $c$ , 1.05 in chloroform). The reported values for this compound (159) are 179-180° and 108.4°, respectively.

Hydrogenolysis of 15 mg of the material in ethanol (15 ml) containing 10 mg of palladium-on-charcoal (5%) was complete after twelve hours. The product was methyl 2-deoxy- $\alpha$ -D-galactopyranoside, XLIV,  $[\alpha]_D$  69.5° ( $c$ , 2.20 in methanol). Reported value (159) 71.8°. As the latter substance had an  $R_f$  of 0.46, the other sugar (with  $R_f$  0.39) is therefore methyl 2-deoxy- $\beta$ -D-galactopyranoside, XLVII. The latter, also obtainable on hydrogenolysis of XLV or LVI in the manner described in section C-I, had a specific rotation of 2.0° ( $c$ , 1.32 in methanol). Reported value (159) for XLVII is 0°.

### E. Reactions of 3,4-Dihydropyran

#### I. "Indirect" bromomethoxylation

1. cis- and trans-2,3-Dibromotetrahydropyran (LX and LXI respectively)

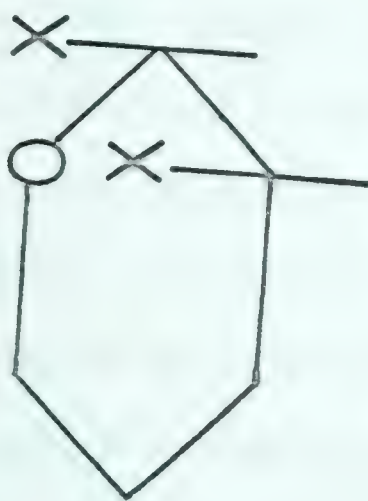
Bromination of dihydropyran in the usual manner (section A) gave a liquid whose n.m.r. spectrum (Fig. 2c) showed signals at very low field, 3.24 and 3.45 tau, arising from the C-2 protons of two configurational isomers LXI and LX, respectively. The former comprised 89% of the reaction product and the coupling constant ( $J_{23}$ ) of less than 1.0 c.p.s. indicated that the 2- and 3-hydrogens were in equatorial-equatorial relationship. In addition, the absence



Reaction Products from 3,4-Dihydropyran

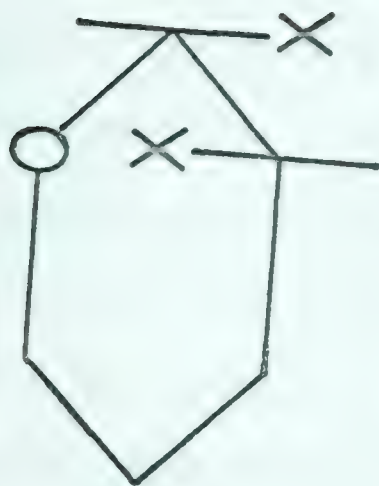


XIX



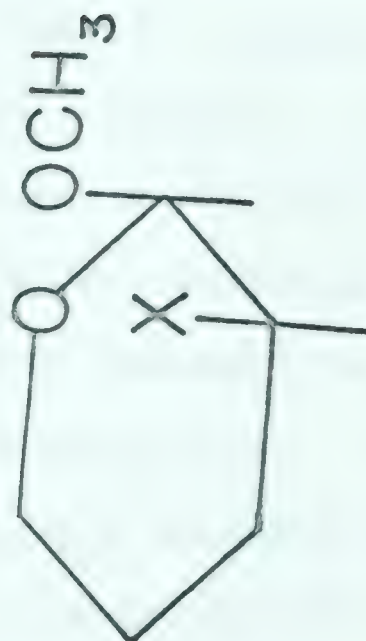
LX X = Br

LXIV X = Cl



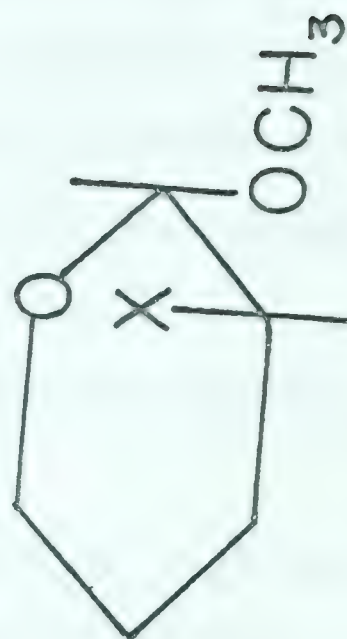
LXI X = Br

LXV X = Cl



LXII X = Br

LXVI X = Cl



LXIII X = Br

LXVII X = Cl

LXVIII X = I

PLATE III



of large coupling for H-3 (at 5.36 tau) indicates that the 3-hydrogen is in gauche relationship with both hydrogens on carbon-4, as well as with the 2-hydrogen. The major compound was therefore the trans-dibromide LXI or its mirror image which would give an identical spectrum. The other dibromide is therefore necessarily the cis-adduct IX or its mirror image, and the observed coupling constant of 3.0 c.p.s. supports the equatorial-axial relationship for H<sub>2</sub> and H<sub>3</sub> in LX. The oily reaction product was subjected to vacuum distillation at 10 mm and 86°, but fractionation was not achieved,  $n_D$  1.4642.

2. cis- and trans-3-Bromo-2-methoxytetrahydropyran (LXII and LXIII respectively)

The product of methanolysis of the dibromides LX and LXI was obtained in 86% yield. The material was a pungent oil whose n.m.r. spectrum (Fig. 14a) indicated that it contained 86% of methoxyl containing material. This was isolated by preparative vapour phase chromatography on a column of Apiezon M (20%) on Chromosorb W operating at 180°. The 100 Mc.p.s. n.m.r. spectrum of the material, which is superimposed in Fig. 14a, showed two distinct signals at 5.45 and 5.54 tau (overlapping at 60 Mc.p.s.) which arose from the 2-hydrogen of two isomeric 3-bromo-2-methoxytetrahydropyrans, LXII and LXIII, respectively. The former, which made up 42% of the mixture, showed a coupling constant ( $J_{23}$ ) of 2.7 c.p.s., and its methoxyl resonance was at 6.35 tau. In the major component, LXIII, the corresponding values were 3.90 c.p.s. and 6.34 tau. The boiling point of the mixture was nevertheless very sharp; 161° at 723 mm, 78° at 10 mm,  $n_D$  1.4841. Efforts to achieve separation by vapour phase chromatography were equally





Products from "Indirect" Bromomethoxylation of 3,4-Dihydropyran  
 Fig. 14a neat liquid Fig. 14b In Polar Medium

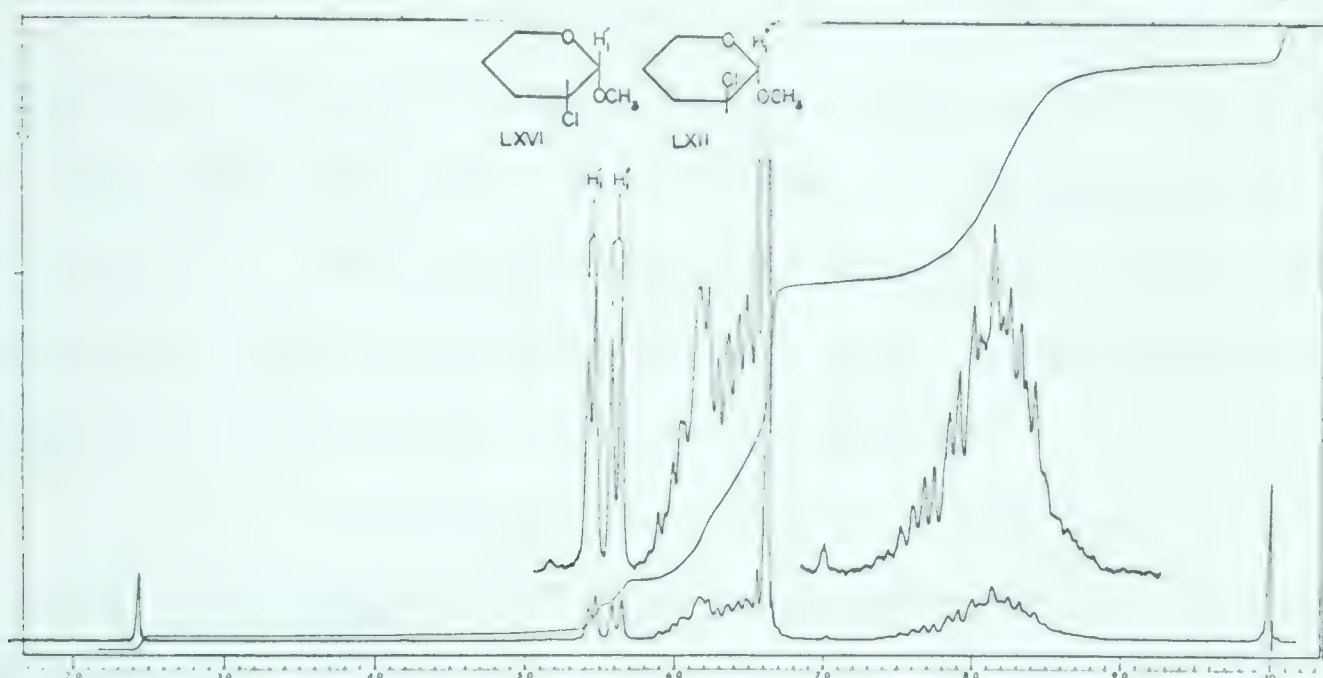


Fig. 14c Products from "Indirect" Chloromethoxylation of 3,4-Dihydropyran

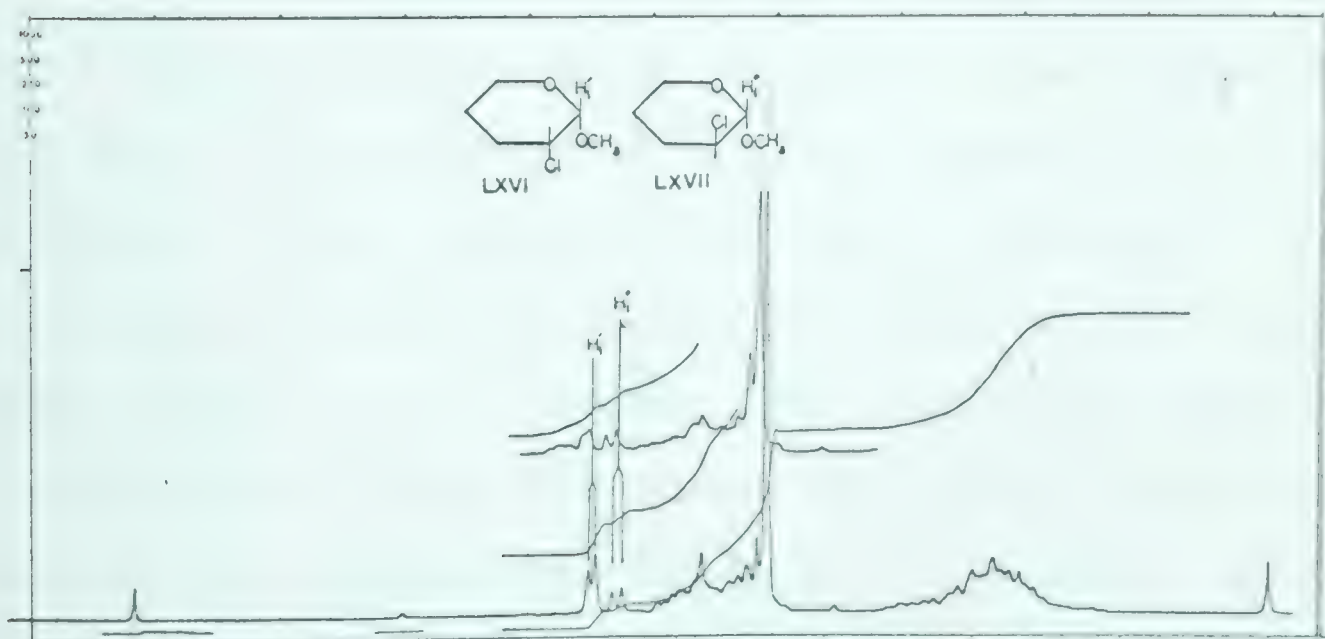


Fig. 14d Products from Methanolysis of trans-2,3-Dichloro-tetrahydropyran



fruitless. When the n.m.r. spectrum was taken in a polar medium of acetonitrile saturated with tetra-N-ethylammonium bromide, the "anomeric" signal ( $H_2$ ) for the major component LXIII increased to 5.0 c.p.s. while that for the minor component remained unchanged (Fig. 14b). The major component, LXIII, was assigned the trans configuration and this assignment along with those for the analogous halogenomethoxides is defended on p. 85 ff.

## II. "Direct" Bromomethoxylation

1. cis- and trans-3-Bromo-2-methoxytetrahydropyran (LXII and LXIII respectively)

"Direct" bromomethoxylation of dihydropyran afforded an oily product (Fig 15a) whose physical constants were identical to those reported above for the mixture of LXII and LXIII. Estimation by n.m.r. (HR 100) showed that the trans-bromomethoxide LXIII (see above) had been formed in much greater concentration (87%) than in the above described "indirect" reaction.

## III. "Indirect" Chloromethoxylation

1. cis- and trans-2,3-Dichlorotetrahydropyran (LXIV and LXV respectively)

Chlorination of dihydropyran produced what was ostensibly a single substance since the product was vacuum distilled at  $37^\circ$  and 3.8 mm without boiling point spread,  $n_D$  1.4935. In addition the n.m.r. spectrum (Fig. 16a) at 60 Mc.p.s. showed only one signal for a strongly deshielded proton at 3.94 tau with a spacing of 2.5 c.p.s. However, the 100 Mc.p.s. spectrum, which is superimposed in Fig. 16a showed this signal to be a multiplet that could not be accounted for by a single proton. It was therefore concluded that chlorination had produced both cis-and



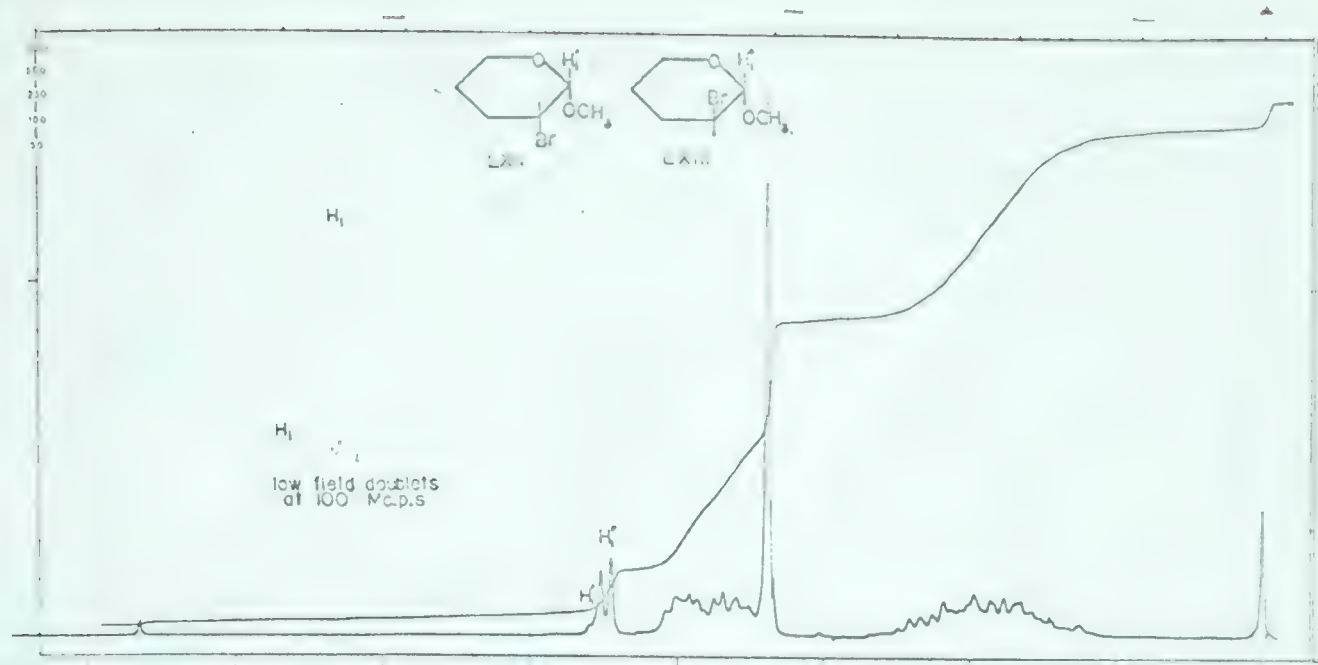


Fig. 15a Products from "Direct" Bromomethoxylation of 3,4-Dihydropyran

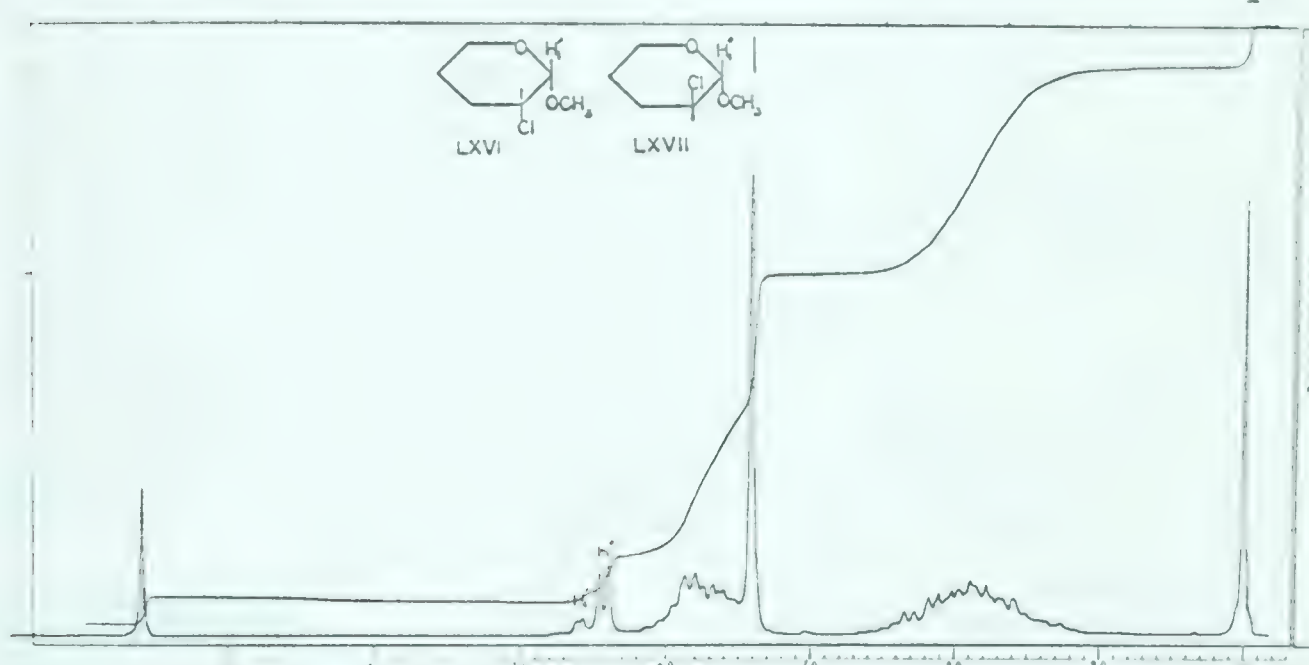


Fig. 15b Products from "Direct" Chloromethoxylation of 3,4-Dihydropyran

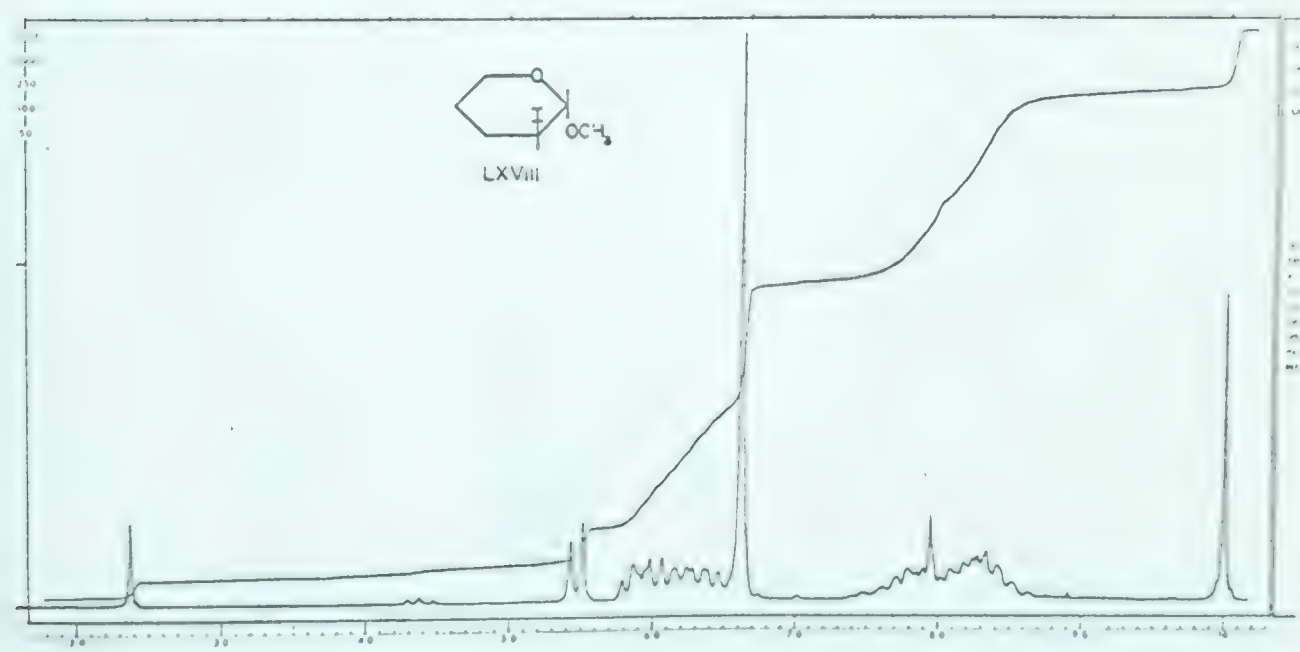


Fig. 15c Products from "Direct" Iodomethoxylation of 3,4 Dihydropyran



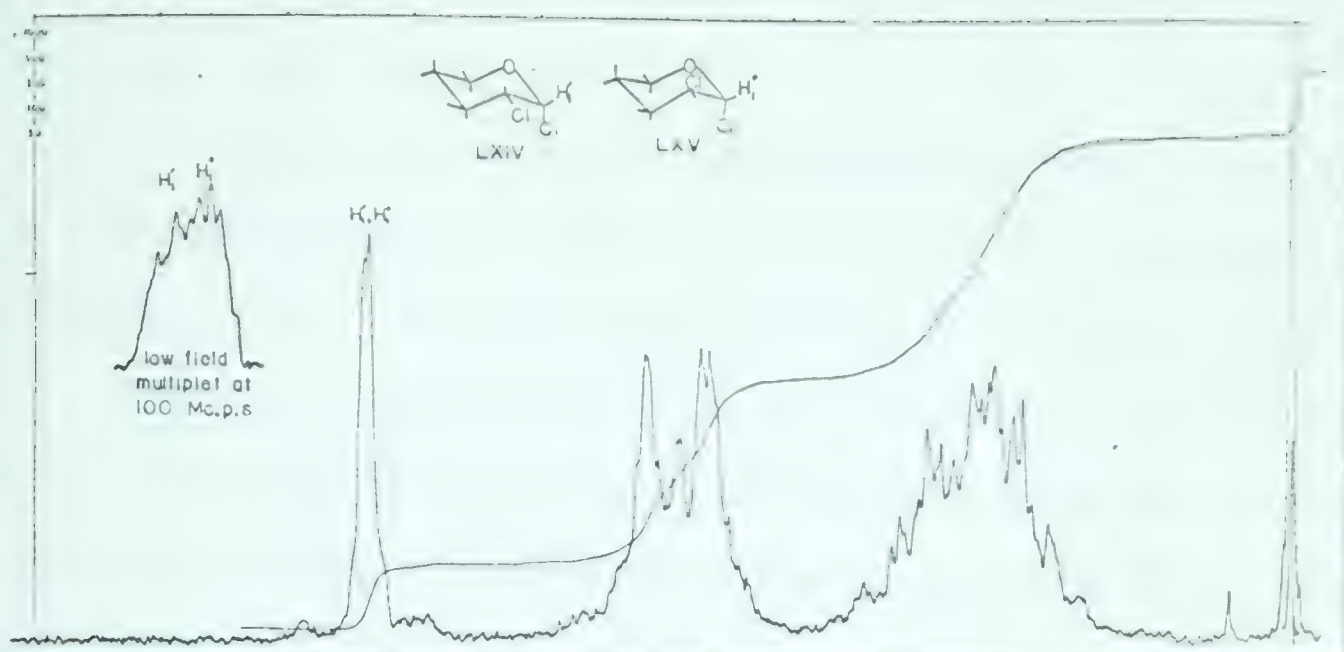


Fig. 16a cis- and trans-2,3-Dichlorotetrahydropyrans

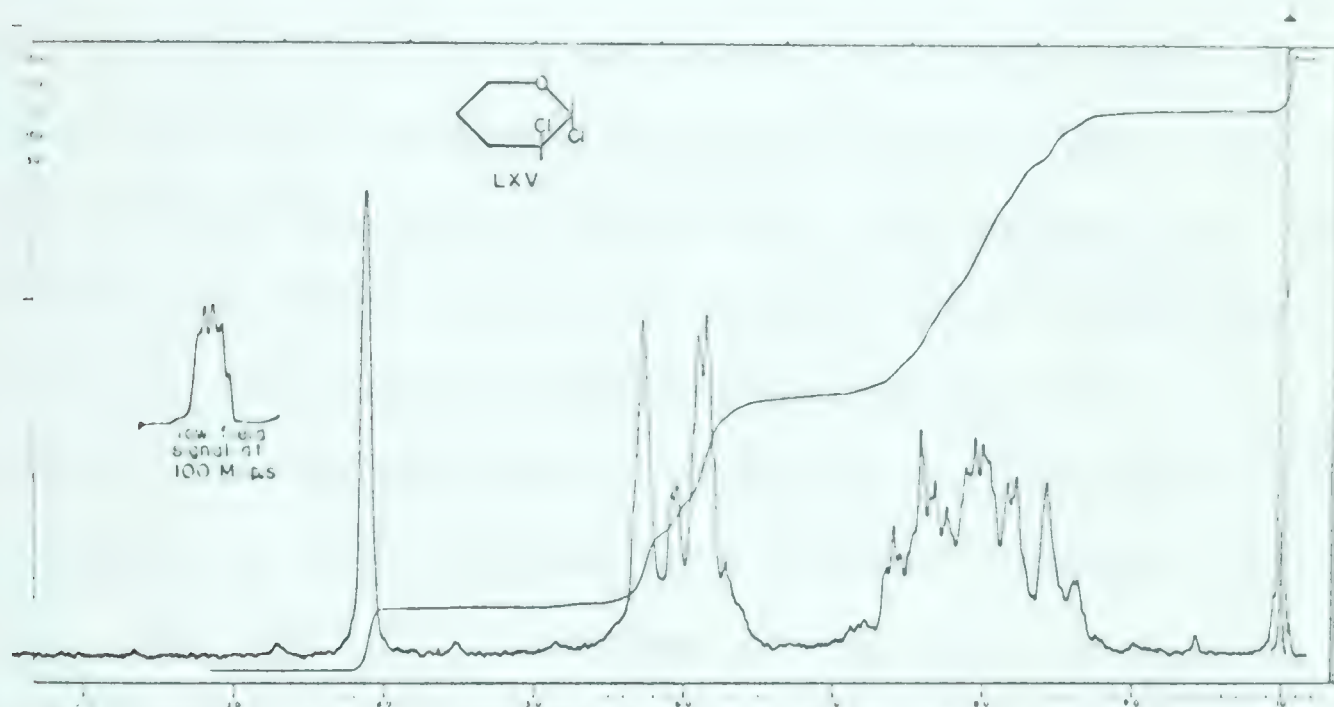


Fig. 16b trans-2,3-Dichlorotetrahydropyran

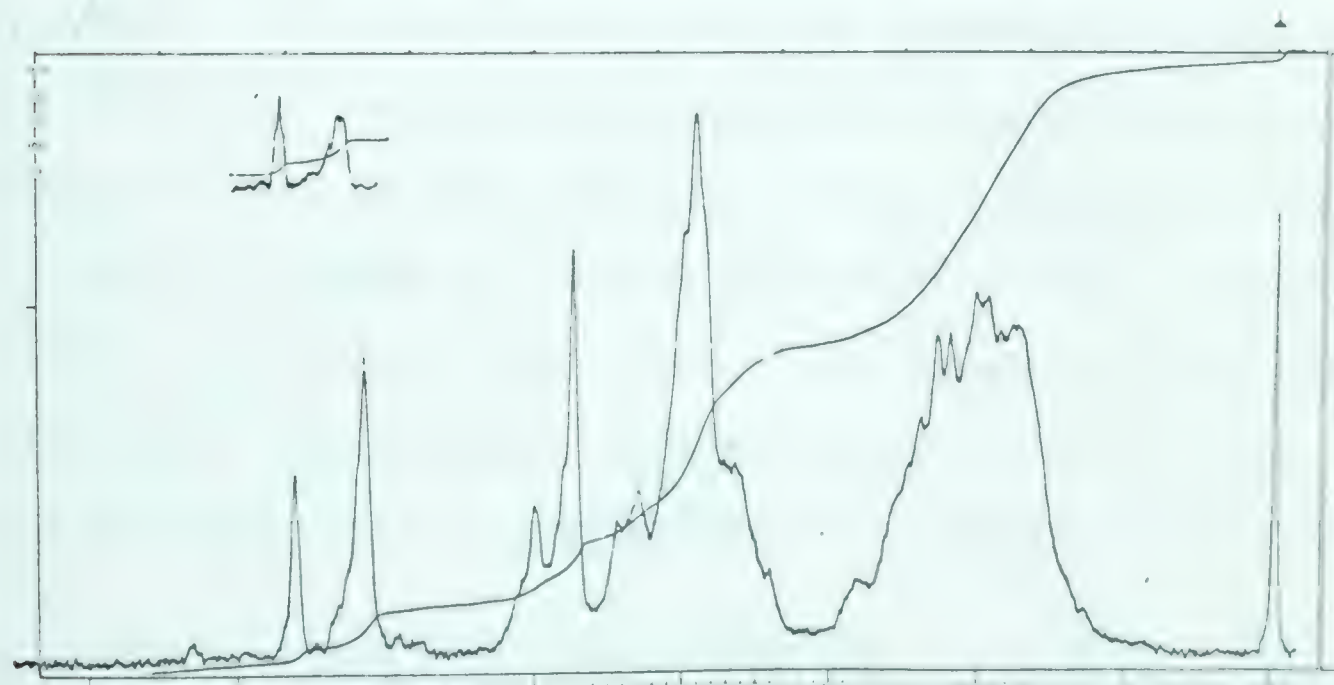


Fig. 16c Equilibration of 2,3-Dichlorotetrahydropyrans

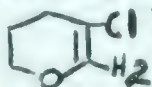


trans-adducts LXIV and LXV and that their signals for the 2-hydrogen were overlapping at 3.94 tau.

It was surmised that equilibration with chloride ions would lead exclusively to one or other isomer - presumably the trans-isomer LXV. In pursuance of this possibility the reaction product from chlorination, 5.0 g, was diluted with 5 ml of acetonitrile and saturated with tetra-N-ethylammonium chloride, and an immediate change in the appearance of the low field signal was noted and was followed on the n.m.r. spectrometer. After 1.5 hours, optimum change had occurred, and prolonged treatment caused the appearance of a new signal at 3.4 tau Fig. 16c.\* Acetonitrile was evaporated from the mixture under reduced pressure and the residue was dissolved in ether and washed with water. The material recovered from the dried ether solution was distilled and the substance which boiled between 35 and 37° at 2.7 mm was collected. The product was evidently a 2,3-dichlorotetrahydropyran because of its reaction with methanol (section E-III 2).

The A60 n.m.r. spectrum of the "new" dichloride (Fig. 16b) is contrasted in Fig. 16 with that of the original product of chlorination. The assignments for the trans-dichloride were adduced by double irradiation experiments on the 100 Mc.p.s. spectrum, Fig. 17a, of the material. Thus a side band 167 c.p.s. upfield from H<sub>2</sub> caused the latter to collapse from a quintet (Fig. 17b) to a triplet (Fig. 17c). Collaterally this finding (a) established the coupling constant (J<sub>23</sub>) to be 1.5 c.p.s. as expected for hydrogens in gauche equatorial-equatorial relationship

\* This probably arose from the 2-hydrogen of 3-chloro-2,6-dihydro-1,4-H-pyran





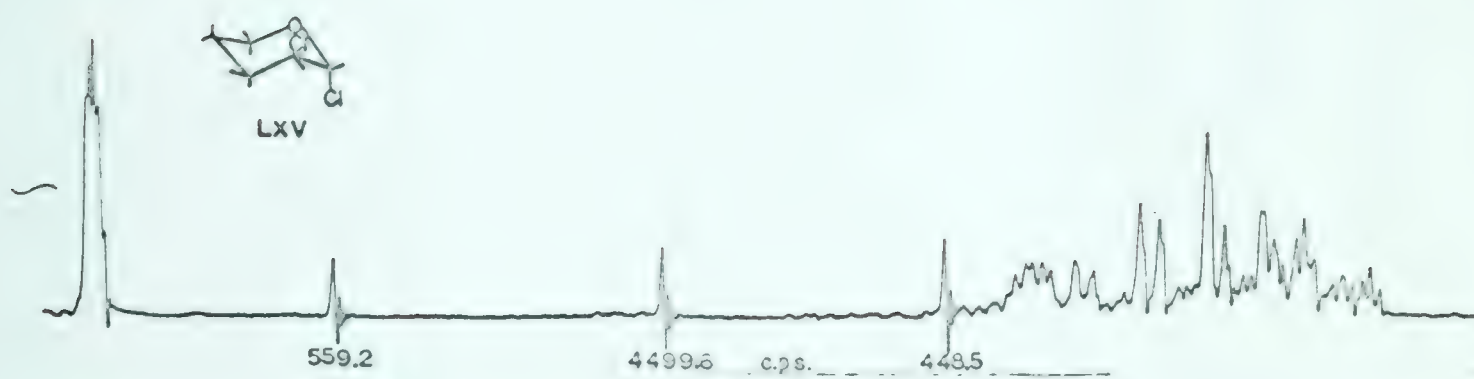


Fig. 17a trans-2,3-Dichlorotetrahydropyran (100 Mc.p.s.)



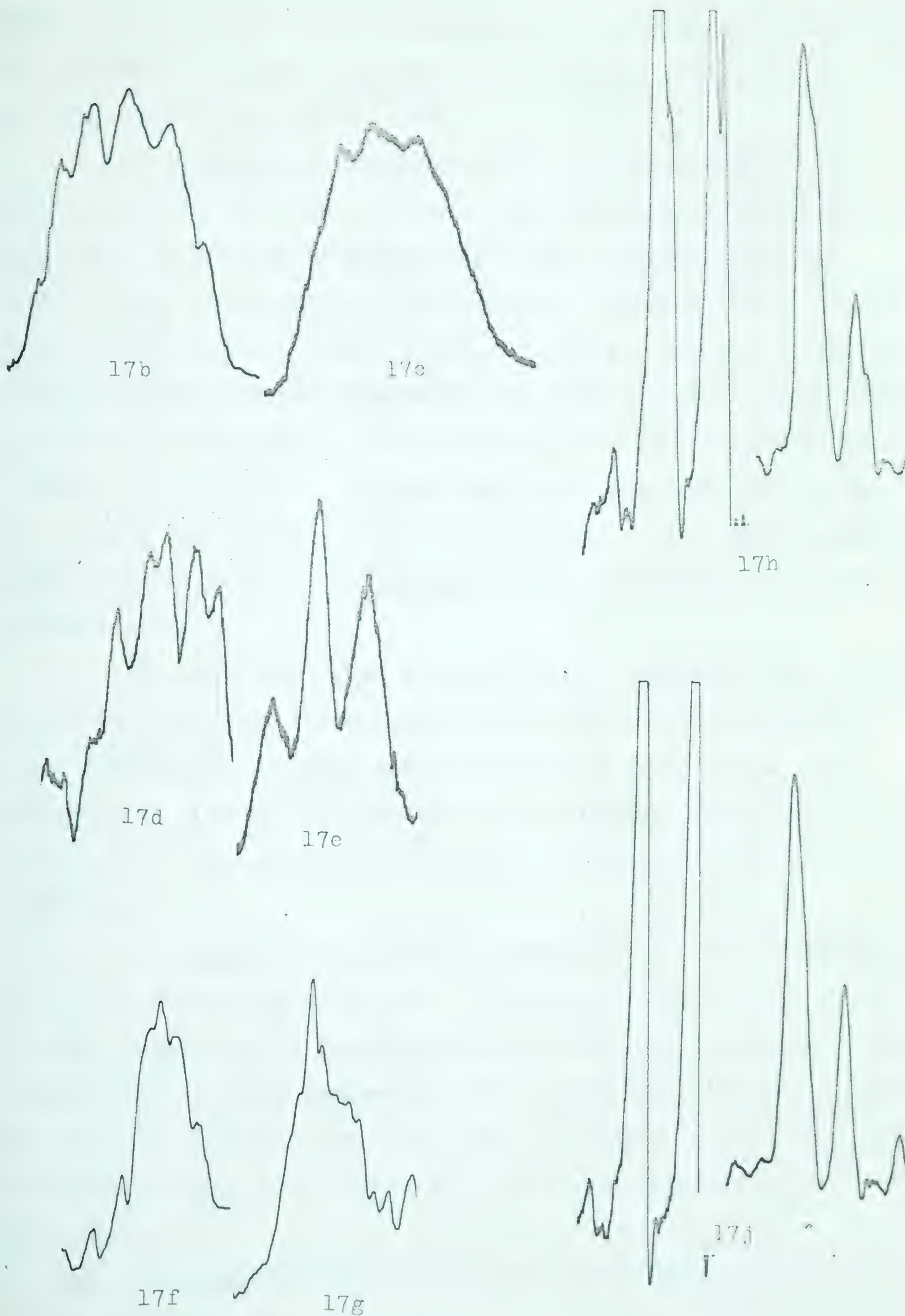


Fig. 17 b -j Decoupling Experiments on trans-2,3-Dichlorotetrahydropyran



(128), and (b) indicated the assignment for  $H_3$  as shown in Fig. 17a. Thus irradiation of the  $H_2$  caused  $H_3$  to collapse from a sextet (Fig. 17d) to a triplet (Fig. 17e).

An independent verification for the assignment of  $H_3$  derives from the fact that the axial proton on the neighbouring carbon will be shifted to higher field than the gem-equatorial proton. Thus irradiation of the methylene envelope [This portion of the spectrum is not shown in Fig. 17.] 157 and 197 c.p.s. upfield caused decoupling of the equatorial and axial protons, respectively, of carbon-4, as adduced by the collapse in the fine structure of  $H_3$  (Figs. 17f and 17g). It was shown simultaneously that  $H_3$  was coupled equally (3.24 c.p.s.) to both protons. All these considerations therefore point to the trans-diaxial arrangement for both chlorines in LXV.

The additional fine structure on  $H_2$  indicates that it is coupled at long range through the lactol oxygen to the hydrogens at the 6-position. Consequently irradiation of  $H_2$  caused disappearance of some of the shoulders on the signals for these protons (Fig. 17h and Fig. 17j), which are located in the vicinity of 380 p.p.m.

The trans-isomer could be produced much more efficiently by high temperature chlorination. Dihydropyran (5.0 g) in 10 ml of carbon tetrachloride was chlorinated in the usual manner. The reaction mixture after saturation with chlorine was sealed, protected from light and immersed for four hours in a water bath at 78°. The fraction which distilled at 37° and 2.7 mm, yielded 6.49 (70%) of pure LXV.

2. cis- and trans-3-Chloro-2-methoxytetrahydropyrans (LXVI and



LXVII respectively)

The product of methanolysis of the dichloride mixture (LXIV and LXV) was judged to be a 1:1 mixture of two isomers of 3-chloro-2-methoxytetrahydropyran. The doublets in the n.m.r. spectrum (Fig. 14c) for the 2-hydrogen were at 5.42 and 5.57 tau, with spacings of 3.0 and 4.0 c.p.s., respectively. By comparison with the iodo- and bromo-analogues (p. 85 ff) the signal to lower field was assigned to the cis-derivative LXVI, and the other to the trans- LXVII. The mixture boiled at 68-70° at 10 mm without fractionation,  $n_D$  1.4565.

Similar methanolysis of the trans-dichloride, LXV, gave the cis- and trans-chloromethoxides, LXVI and LXVII, in 70 and 30% relative amounts, respectively, Fig. 14d.

#### IV. "Direct" Chloromethoxylation

1. cis- and trans-3-Chloro-2-methoxytetrahydropyran (LXVI and LXVII, respectively)

"Direct" chloromethoxylation of dihydropyran proceeded in 93% yield to give a 1:3 mixture of the cis- and trans-derivatives LXVI and LXVII which had identical physical constants to the similar mixture obtained in the "indirect" reaction. The n.m.r. spectrum of the mixture is shown as Fig. 15b.

#### V. "Direct" Iodomethoxylation

1. trans-3-Iodo-2-methoxytetrahydropyran (LXVIII)

The iodomethoxylation of dihydropyran gave a product in 90% yield which was distilled under vacuum, 9 mm at 84°,  $n_D$  1.5177. The material contained a single component whose n.m.r. signal (Fig. 15c) for the 2-hydrogen at 5.48 tau was a doublet with spacing 5.0 c.p.s., and because of this it was judged to be trans-3-iodo-2-methoxy tetrahydropyran (See discussion p. 81 ff).



	C.S.-	J <sub>12</sub>	C.S.	J <sub>23</sub>	C.S.	J <sub>34</sub>	C.S.	J <sub>45</sub>	C.S.	comments
	5.54	4.0	6.0 to 6.4 *	1.0	5.02	9.0	4.75	9.0	6.40	* H <sub>2</sub> not distinctly chemically shifted from H <sub>5</sub>
	5.45	9.0	6.0 to 6.4 *	9.0	5.00	9.0	4.62	9.0	6.38	
	5.45	9.0	6.0 to 6.4 *	9.0	5.06	9.0	4.63	9.0	6.42	
	5.51	8.0	6.12	11.0	4.92	4.0	4.62	10.2	6.42	
	5.46	8.5	6.03	10.3	4.88	3.5	4.60	10.2	6.41	
	5.40	8.5	5.6 to 6.0 *	10.2	H <sub>3</sub> not distinctly chemically shifted from H <sub>4</sub>				6.42	

TABLE I

C.S. = Chemical shift in tau values

R = Ac

J = coupling constants in c.p.s.



	H <sub>1</sub>			H <sub>2</sub>			H <sub>3</sub>			H <sub>4</sub>			C.S.	comments
	C.S.	J <sub>12</sub>	C.S.	J <sub>23</sub>	C.S.	J <sub>34</sub>	C.S.	J <sub>45</sub>						
	5.09	< 1	5.56	*			** H <sub>3</sub> and H <sub>4</sub> lie between 4.52 and 4.66 tau				6.55	* not ascertained		
	5.05	< 1	5.54	*			H <sub>3</sub> and H <sub>4</sub> lie between 4.68 and 4.82 tau				6.57	** H <sub>2</sub> not distinctly chemically shifted from H <sub>4</sub>		
	4.91	1.27	5.47	4.56				8.65	4.65	10.2	6.57			
	4.88	1.1	5.62	*			H <sub>3</sub> and H <sub>4</sub> lie between 4.3 and 4.5 tau				6.58			
	4.85	1.5	5.73	*			H <sub>3</sub> and H <sub>4</sub> lie between 4.5 and 4.8 tau				6.58			
	4.77	1.12	5.60	4.50						1.1	6.75			

C.S. = Chemical shift in tau values TABLE II

J = coupling constants in c.p.s.

R = Ac



N.M.R. analysis of methyl 2-bromo-2-deoxy- $\beta$ -D-mannopyranoside and methyl 2-chloro-2-deoxy- $\alpha$ -D-galactopyranoside triacetates

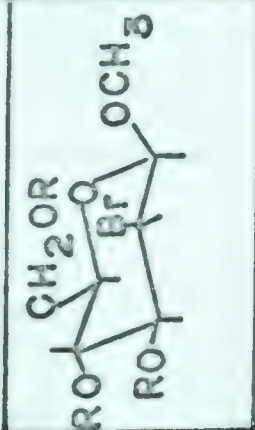
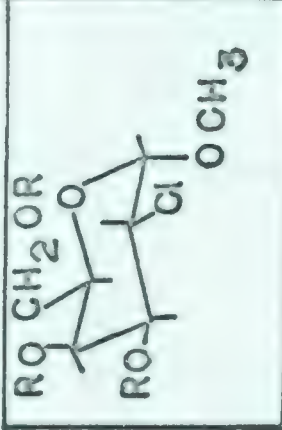
H <sub>1</sub>		H <sub>2</sub>		H <sub>3</sub>		H <sub>4</sub>		OCH <sub>3</sub>		comments
C.S.	J <sub>12</sub>	C.S.	J <sub>23</sub>	C.S.	J <sub>34</sub>	C.S.	J <sub>45</sub>	C.S.		
	5.52	1.5	5.45	4.5	5.02	0.0	4.57	10.0	6.3	* H <sub>2</sub> not identified; probably from H <sub>3</sub>
	5.50	3.8	5.5*		** H <sub>3</sub> and H <sub>4</sub> lie between 4.26 and 4.45 tau				6.62	** H <sub>3</sub> not identified; probably from H <sub>4</sub>

TABLE III

C.S. = Chemical shift in tau values

J = coupling constants in c.p.s.

R = Ac



# Stereochemical Routes of Reaction

Reactant	Reaction	Percent Yield and Configuration of Products			
		1,2-Trans-Diaxial	1,2-trans-Diequatorial	cis-1-Axial-2-Equatorial	cis-1-Equatorial-2-Axial
D-Glucal Triacetate	Chlorination*	---	---	100 (XXIX)	---
	Chloromethoxylation*	51 (XXXIII)	41 (XXX)	8 (XXXII)	---
	Bromination*	30 (XXI)	---	60 (XXIII)	---
	Bromomethoxylation*	66 (XXVIII)	33 (XXV)	---	---
	Iodomethoxylation	66 (XXXVIII)	33 (XXXVI)	---	---
D-Galactal Triacetate	Chlorination	---	---	100 (XLIX)	---
	Chloromethoxylation*	8 (LII)	53 (LI)	39 (LI)	---
	Bromination*	50 (XLII)	---	50 (XLI)	---
	Bromomethoxylation*	52 (XLIII)	37 (XLV)	11 (XLVIII)	---
	Iodomethoxylation	81 (LVI)	19 (LV)	---	---
3,4-Dihydro-pyran	Chlorination	** (LXV)	---	** (LXIV)	---
	Chloromethoxylation*	50 (LXVII)	---	25 (LXVI)	---
	Bromination*	75 (LXI)	---	11 (LX)	---
	Bromomethoxylation*	87 (LXIII)	---	13 (LXII)	---
	Iodomethoxylation	100 (LXVIII)	---	---	---

T A B L E I V

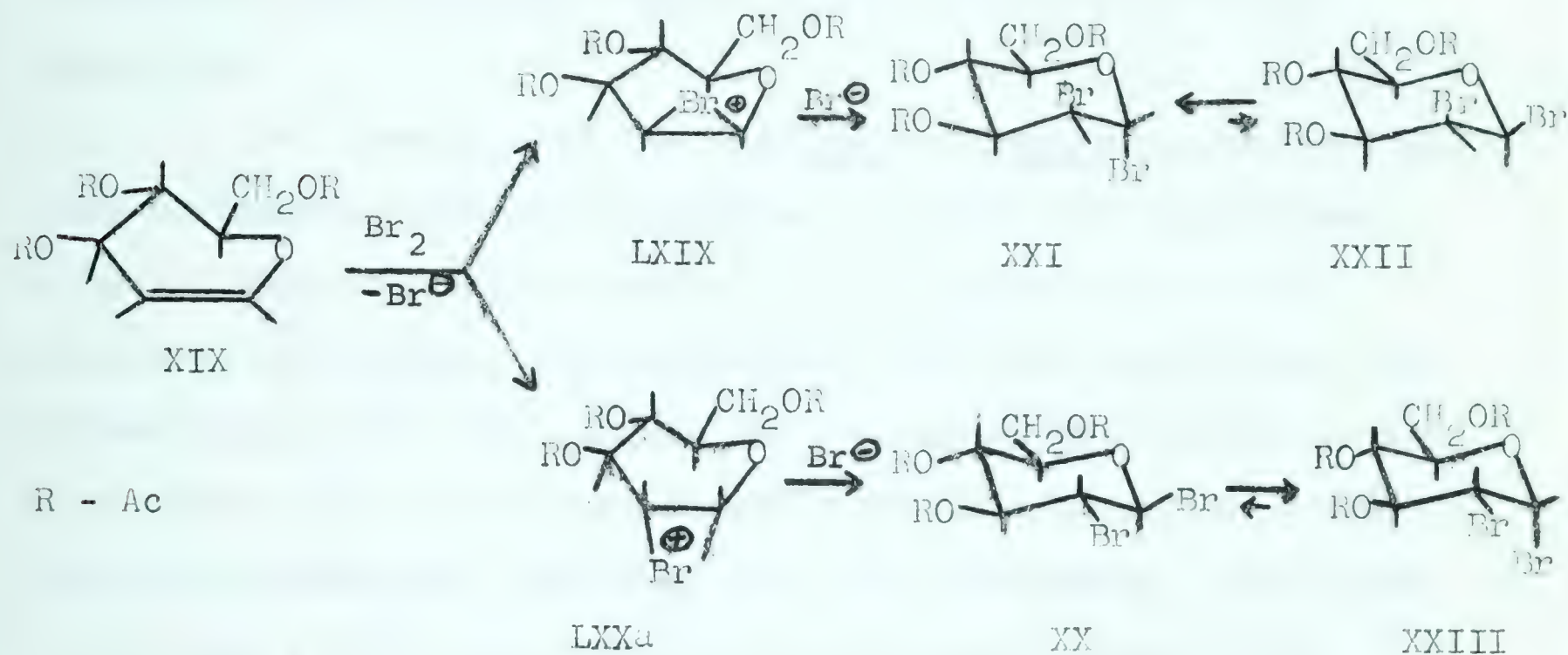
\* Direct halogenomethoxylation

\*\* Judged from the composition of the product obtained on reacting the dichloride with methanol in the presence of silver carbonate



# DISCUSSION OF RESULTS

It was discussed in the introduction that nucleophilic attack on the 1,2-halonium ions of vinyl ethers will always occur at the carbon bonded to the oxygen. If the bromination of D-glucal triacetate (XIX) followed the classical steric course, the cyclic



ions LXIX and LXX, formed in the initial step, would be attacked by the bromide ion at carbon-1 to give the trans-adducts XX and XXI. However, this was not the case. The product of bromination on examination by n.m.r. (Fig. 2a) contained two components, the major one of which (XXIII) gave a doublet at 3.53 tau with a spacing of 3.5 c.p.s. The other component, XXI, produced a doublet at 3.35 tau with a spacing of 1.0 c.p.s. The general experience with n.m.r. spectra (52) of acetylated glycosyl bromides clearly indicated that both these doublets, because of their chemical shifts, arose from anomeric hydrogens in equatorial orientation.



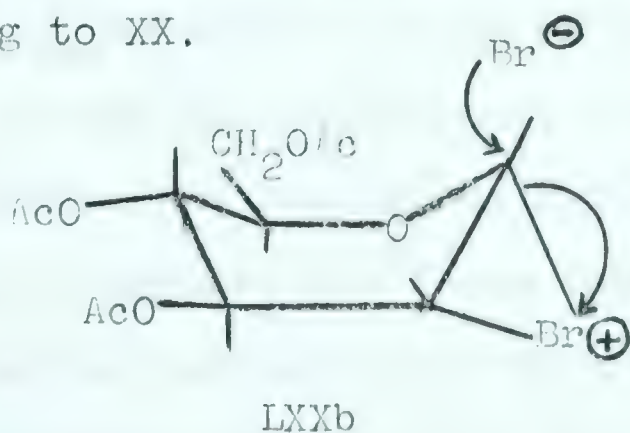
Since, in general, derivatives of  $\alpha$ -D-glucofuranose and  $\alpha$ -D-mannofuranose provide signals for the anomeric hydrogens with spacings of 3.0-3.6 c.p.s. and 1.0-1.5 c.p.s., respectively, the spacings indicated that the compounds XXIII and XXI possessed the 1,2-cis- $\alpha$ -D-gluco and 1,2-trans- $\alpha$ -D-manno-configurations, respectively. As will be seen below, this conclusion was confirmed through characterization of the products formed on the methanolysis of the dibromides.

The formation of the 1,2-trans- $\alpha$ -D-manno dibromide (XXI) is in accordance with the stereochemical route anticipated on classical grounds. It is now well established that, in the absence of large axial substituents at the 3 or 5 positions, the thermodynamically stable anomer for glycopyranosyl halides is the anomer which has the halogen in axial orientation. The favorable coulombic interaction resulting from this arrangement (see Scheme 1) can provide a driving force of 1.5 to 2.0 kcal/mole (70,71). The formation of the  $\alpha$ -D-mannosyl bromide (XXI) has the advantage of this effect, and furthermore its formation should be enhanced by the fact that cyclic oxonium ions open preferably in the diaxial mode (85-88).

The formation of the 1,2-cis- $\alpha$ -D-glucosyl bromide, XXIII, as the main product of the reaction is not in keeping with the classical stereochemical route. It is conceivable that the  $\beta$ -D-gluco dibromide (XX) may have formed originally, and was driven by the anomeric effect to the  $\alpha$ -anomer (XXIII). If this were the case, the n.m.r. spectrum of the reaction mixture should show initially a signal for an axial anomeric proton at higher field, about 4.5 tau, with a spacing of about 8 c.p.s. With



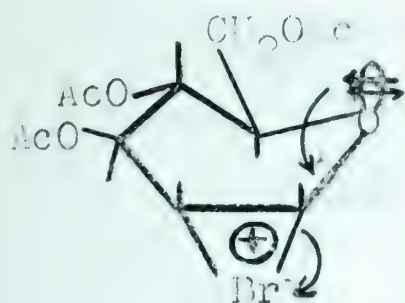
tetra-O-acetyl- $\beta$ -D-glucopyranosyl chloride, for example,  $H_1$  is a doublet of 9 c.p.s. spacing at 4.7 tau. The disappearance of the signal as the compound (XX) anomerized would then coincide with an increase in the intensity of the doublet for XXIII at 3.53 tau. However, when the spectrum was measured within fifteen seconds of the addition of bromine, the equilibrium mixture had already been established; and the possibility that this anomerization could have occurred so much more rapidly than analogous reactions (77) seems remote. The possibility that excess bromine in the reaction mixture was catalyzing the transformation (23, 160) was eliminated since the equilibrium was as rapidly attained when there was a deficiency of bromine. It therefore appears that, if formed at all, the gluco cyclic ion, LXX, does not exist long enough for  $\beta$ -attack by a bromide ion. It is to be noted in this respect that nucleophilic attack at the anomeric centre of LXXa must lead to diequatorial opening of the bromonium ion. Presumably, the ion must assume a conformation tending toward the boat form (LXXb) for the attack leading to XX.



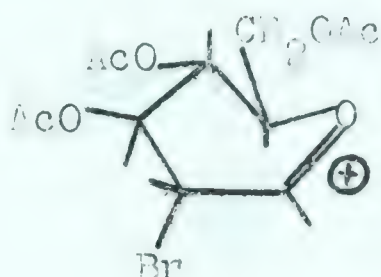
Glycosyl oxocarbenium ions have been suggested previously as intermediates in reactions involving the anomeric centre (71, 77, 161-163) and it is probable that they might also be intermediates here. Thus, if the gluco bromonium ion (LXX) had only a fleeting existence and was rapidly converted to the gluco oxocarbenium ion



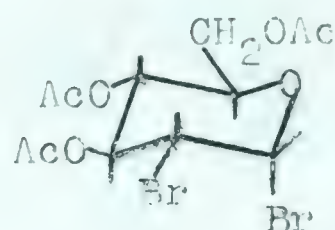
(LXXI), the incoming bromide ion would no longer be constrained



LXX



LXXI

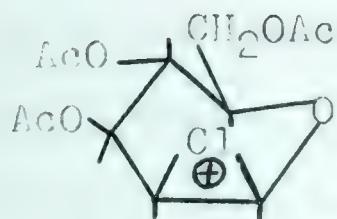


XXIII

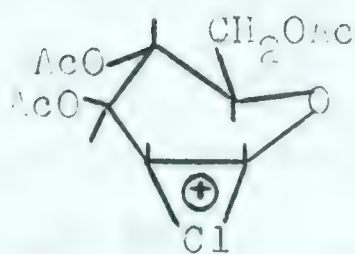
to attack leading to  $\beta$ -anomer. Electron release from the oxygen to the  $\alpha$ -D-glucosyl ion (LXX) would be in the nature of a trans-diaxial elimination, and would tend to favor the formation of the oxocarbenium ion LXXI. The planar nature of the new intermediate now enables the anion to respond to the driving force of the anomeric effect which should operate in the transition state. As will be seen, similar arguments relating to the galactose analogues may be advanced. Hence, the intermediate cations may be LXIX and LXXI. The  $\beta$ -mannosyl cation (LXIX) does not have a p-orbital of the lactol oxygen suitably oriented for participation in an opening of the bromonium ion to form oxocarbenium ion. It is conceivable, therefore, that trans-diaxial opening of the bromonium ion, as discussed above, is the favorable route of reaction.

The results obtained on the chlorination of D-glucal triacetate appear to support the above interpretations. The chlorination in carbon tetrachloride gave only the 1,2-cis- $\alpha$ -D-glucosyl chloride (XXIX) shown in Fig. 6a. The formation of the cyclic cation implies that the halogen is capable of accommodating a positive charge. It is known (73-76) that in comparison with iodine and bromine, chlorine forms a poor cation. Therefore the oxocarbenium ion (LXXIII) should be much more favorable than either of the chloronium cations LXXIIa or LXXIIb, and it (LXXIII) may

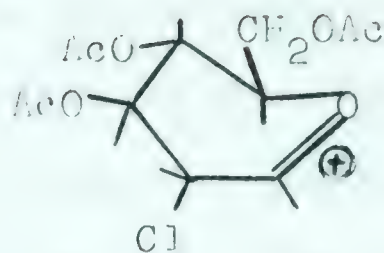




LXXIIa



LXXIIb



LXXIII

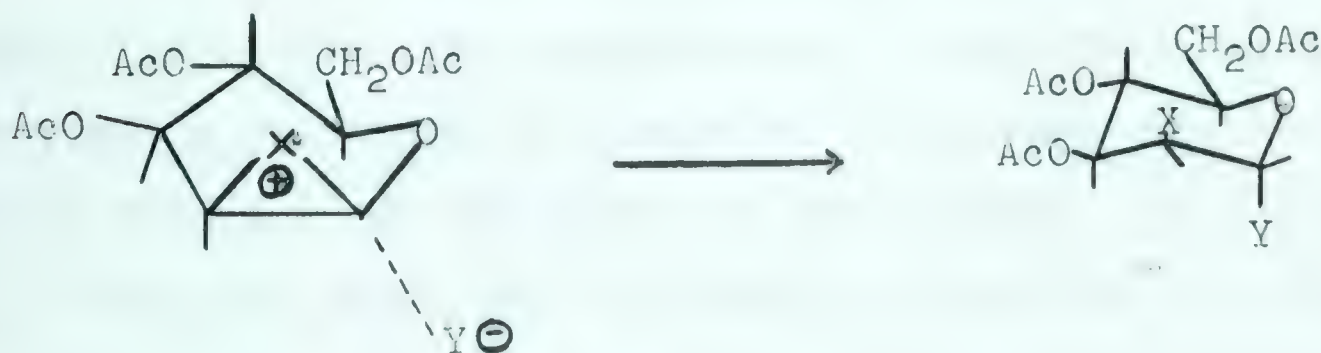
therefore arise directly from electrophilic attack by the chlorine. In this case, the ion LXXIII would be the sole reaction intermediate and for the reasons discussed above relating to the formation of XXIII, it is not surprising that the  $\alpha$ -glucosyl chloride (XXIX) was the sole product of the reaction. The halogenations of D-galactal triacetate present a similar picture. Bromination produced a 1:1 mixture of the 1,2-trans- and 1,2-cis-derivatives (Fig. 2b) of related configuration, namely 2-bromo-2-deoxy-3,4,6-tri-O-acetyl- $\alpha$ -D-talo- (XLII) and  $\alpha$ -D-galactopyranosyl bromide (XLI). As in the glucose case, chlorination gave the cis- adduct XLIX as the only product, Fig. 6b.

The experimental results of the halogenation reactions of the glycals are summarized in Table IV.

For reasons that will become apparent later on, it was decided to examine the stereochemical routes followed on the reaction of D-glucal triacetate and D-galactal triacetate with halogens (chlorine, bromine and iodine) in methanol containing silver acetate. The results obtained are summarized in Table IV, and proof of the structure of the compounds was offered in the Experimental section. The mechanistic considerations which were presented above in connection with the halogenation reactions, have the same significance for the halogenomethoxylations.



However, the fact that the latter - the "direct" reactions - are done in the polar medium of methanol, whereas the halogenations are done in carbon tetrachloride, should be of enormous significance in reactions such as these which are subject to powerful electronic influences. Thus, on page 70 it was suggested that the cyclic bromonium ion LXX was rapidly converted to the oxocarbenium ion LXXI, but, had the reaction medium been polar, this transformation may have been forestalled. In methanol, once the cyclic ions LXIX and LXX are formed, they would be strongly solvated, and attack by the nucleophilic agent, (the solvent in this case), should lead to the 1,2-trans derivatives. The argument follows from the fact that the direct bromomethoxylation gave the  $\alpha$ -D-manno- and  $\beta$ -D-gluco-derivatives exclusively, with the former predominating. The iodo- and chloro-methoxylations followed virtually the same stereochemical route in spite of the vastly different electronegativities of the halogens (72-76). The  $\alpha$ -D-manno derivatives are favored for the reasons outlined above (p. 69). The transition state leading to them is seen to require a large charge



separation. It is therefore not surprising that the  $\alpha$ -D-manno derivatives were the major products when methanol was the solvent (i.e. in the "direct" halogenomethoxylations), whereas in the



halogenations in carbon tetrachloride, such derivatives were either absent from (in the case of chlorine), or the minor component of (in the case of bromine) the reaction product. Carbon tetrachloride is incapable of solvation and hence does not facilitate a large charge separation. In the bromination of D-glucal triacetate (Fig. 2a) for example, the  $\beta$ -D-manno-adduct (XXI) was produced in only 30% yield whereas in polar methanol (the "direct" reaction) the  $\alpha$ -D-mannoside (XXXVIII) was produced in 60% (Fig. 5a). In the absence of solvation, the best means for stabilization of the intermediates would be that to be found in the anomeric effect. It is undoubtedly for this reason that halogenations in carbon tetrachloride produce only the  $\beta$ -D-anomers. A fortuitous discovery by the author during this investigation seems to give additional support to this view. It was found that the inclusion of collidine in the reaction medium caused an increase in the amount of the 1,2-trans- $\alpha$ -D-isomers ( $\alpha$ -D-manno- or  $\alpha$ -D-talo-) formed in the "direct" reactions. The reason for this has not been investigated.

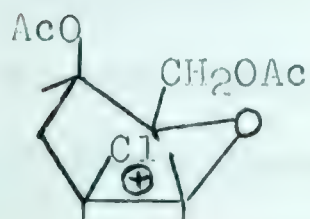
In contrast with the halogenomethoxylation reaction of D-glucal triacetate, the stereochemical routes followed in the corresponding reactions of D-galactal triacetate were found to be strongly dependent on the nature of the halogen. It is quite obvious that the reason for this must be connected with the axial C-4 acetoxy group. The result of the chloromethoxylation of D-galactal triacetate are summarized in Table IV. It will be observed that the products which possessed the 2-chlorine in equatorial orientation, i.e. the  $\alpha$ - and  $\beta$ -galactosides I and II, comprised 47% and 53% respectively, of the reaction product. The 1,2-trans-adduct namely methyl 2-chloro-2-deoxy- $\alpha$ -D-talopyranoside triacetate



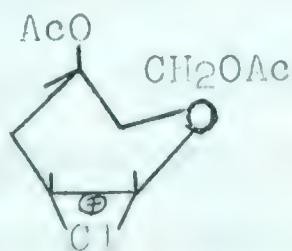
(L11) was produced in only 8% yield.

Bromomethoxylation of D-galactal triacetate produced a slight excess of the 1,2-trans-diaxial adduct (XLII), and the products which possessed the 2-bromine in equatorial orientation i.e. the  $\alpha$ -D- and  $\beta$ -D-galactosides XLVIII and XLV, were produced in 11 and 37% respectively. Iodomethoxylation gave 81% of the 1,2-trans-diaxial  $\alpha$ -D-talo-derivative (LVI) and 19% of the 1,2-trans-diequatorial  $\beta$ -D-galactoside LV.

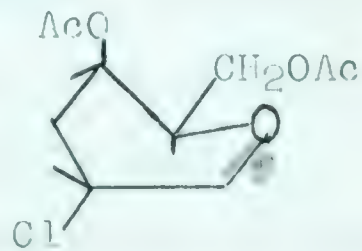
These results seem to imply that the erected acetoxy group in D-galactal triacetate provides a greater steric barrier to chlorine than to the other halogens. Probably the fact that the C - Cl bond is the shortest of the three (134) might cause it to experience the most severe 1-3 interaction with the axial group. Alternatively, or perhaps additionally, the ability for iodine to form a cyclic ion is over a million times as great as with chlorine (73, 165). This enormous stability may therefore compensate for any steric interaction in the cyclic iodonium ion leading to the  $\alpha$ -D-taloside LVI. Furthermore, Dreiding models indicate that in the  $\beta$ -D-talosyl iodonium ion, the carbonyl function of the axial C-4 acetoxy group is suitably poised to enter into a stabilizing electrostatic interaction with the positive iodine. Attack by methanol leading to LVI thereby gains added impetus. Bromine, not surprisingly, falls somewhere between the extremes experienced by iodine and chlorine.



LXXIV



LXXV



LXXVI



If the arguments in the preceding paragraphs are accepted, then the greater steric interaction will cause the chlorine to add from the less hindered underside to give LXXV. Because of the inferior nature of the cyclic chloronium ion (73, 165) participation of electrons in the axial p-orbital of the oxygen (as discussed above) will result in the galactosyl oxocarbenium ion (LXXIV) being the reaction intermediate. In the direct chloromethoxylation reactions of D-galactal triacetate (Fig. 11b), methanol adds irreversibly to each side of the planar system in LXXVI so that the reaction product contains both the  $\alpha$ -D and  $\beta$ -D anomers of methyl 2-chloro-2-deoxy-galactopyranoside triacetates, L and LI. The ratio in which the  $\beta$  and  $\alpha$  anomers were formed (1.36:1) is the same (within experimental error) as that observed (1.43:1) when the  $\beta$ -D-galactoside, L, was anomerized with titanium tetrachloride in refluxing chloroform (section D-IV). The production of only the  $\alpha$ -anomeric chloride, XLIX, (Fig. 6b) in contrast with both the  $\beta$  and  $\alpha$  galactosides (L and LI) in chloromethoxylation is in keeping with general experience and current theory concerning reactions at the anomeric centre. The anomeric effect should cause the halide ion to assume the axial orientation more resolutely than a less polar nucleophile such as methanol. By way of analogy, in its acid catalyzed reaction with methanol, D-galactose gives nearly equal amounts of the alpha and beta pyranosides at equilibrium (166, 167). However, treatment of  $\alpha$ -D-galactose pentacetate with hydrobromic acid produces 90% of tetra-O-acetyl- $\alpha$ -D-galactopyranosyl bromide (168).

A broad comparison therefore seems possible between chlorination and chloromethoxylation of D-galactal triacetate, and



the same appears to hold for the analogous reactions of bromine. In Table IV it is seen that bromination of D-galactal triacetate produced 50% of the 1,2-trans ( $\alpha$ -D-talo) dibromide XIII, (Fig. 2b) while the direct bromomethoxylation produced an equivalent amount (52%) of the corresponding 1,2-trans-bromomethoxide XLII (Fig. 11a). On the other hand, the 50% of 1,2-cis-product (XLI) formed in the bromination is matched by the total amount (48%) of anomeric  $\alpha$  and  $\beta$  2-bromo-2-deoxy-D-galactosides XLV and XLVIII, formed on bromomethoxylation.

The iodomethoxylation reactions of D-galactal triacetate (Fig. 11c) are at the other end of the spectrum of the stereochemical routes (see Table IV). Thus (a) the stability of the cyclic iodonium ion (page 75), (b) the polarity of the solvent, (page 73) and (c) electrostatic interaction with the erected C-4 acetoxy group (page 75) are all in favour of the 1,2-trans-adduct. Not surprisingly therefore, methyl 2-deoxy-2-iodo- $\alpha$ -D-talopyranoside triacetate, LVI, comprised 81% of the reaction product, and the inclusion of collidine in the reaction medium (see page 74) increased its formation to nearly 90%. The formation of the other trans-adduct, methyl 2-deoxy-2-iodo- $\beta$ -D-galactopyranoside triacetate (LV) in only 19% yield reflects the inferiority of the  $\alpha$ -D-galacto-iodonium ion (corresponding to the bromonium ion LXXa in Scheme 6) vis-a-vis its  $\beta$ -D-talo-counterpart (corresponding to the brominium ion LXIX in Scheme 6).

The complete absence of methyl 2-deoxy-2-iodo-3,4,6-tri-O-acetyl-glycosides with the  $\beta$ -D-gluc- and  $\beta$ -D-galacto-configurations in the iodomethoxylation of glucal and/or galactal triacetates respectively, is regarded as proof that oxocarbenium ions are not



formed in these iodination reactions. The reason for this is obviously the stability of the cyclic iodonium ion. Conversely, these arguments support the proposal that the 1,2-cis-adducts in the halogenation and halogenomethoxylation reactions arise from oxocarbonium ions. A logical extension of these arguments would suggest that these species are the crucial intermediates in all reactions which result in the 1,2-cis-arrangement at the anomeric centre. Of the alternatives suggested for these reactions (77), none seems to account as satisfactorily for the experimental results under discussion.

It was suggested in the introduction that the steric course observed on kinetically controlled halogenation of cyclic ketones might be instructive in considering the halogenomethoxylation reactions of D-galactal triacetate. It would appear that some correlation can be found between both categories of reactions. Thus Warnhoff (123) found that chlorination of cholestan-3-ones went with predominant formation of the equatorial 2- $\alpha$ -chloro ketone. Similarly, Nickon and Castle (148) observed the exclusive formation of the 6- $\alpha$ -chloroketone on chlorination of cholestan-7-ones. The "direct" chloromethoxylation of D-galactal triacetate (Fig. 11b) gave comparable results; the products which possessed the 2-chlorine in equatorial orientation, i.e. the  $\alpha$ - and  $\beta$ -galactosides L and LI, comprised 92% of the reaction product.

With regard to bromination Nickon and Castle (148) found that the axial 6- $\beta$ -epimer was formed in a slight excess in the bromination of both cholestan-7-ones and its 6- $\alpha$ -chloro derivative. Similarly the "direct" bromomethoxylation of D-galactal triacetate (Fig. 11a) produced a slight excess of the product containing the



axial 2-bromine, namely: methyl 2-bromo-2-deoxy- $\alpha$ -D-talopyranoside triacetate, XLIII.

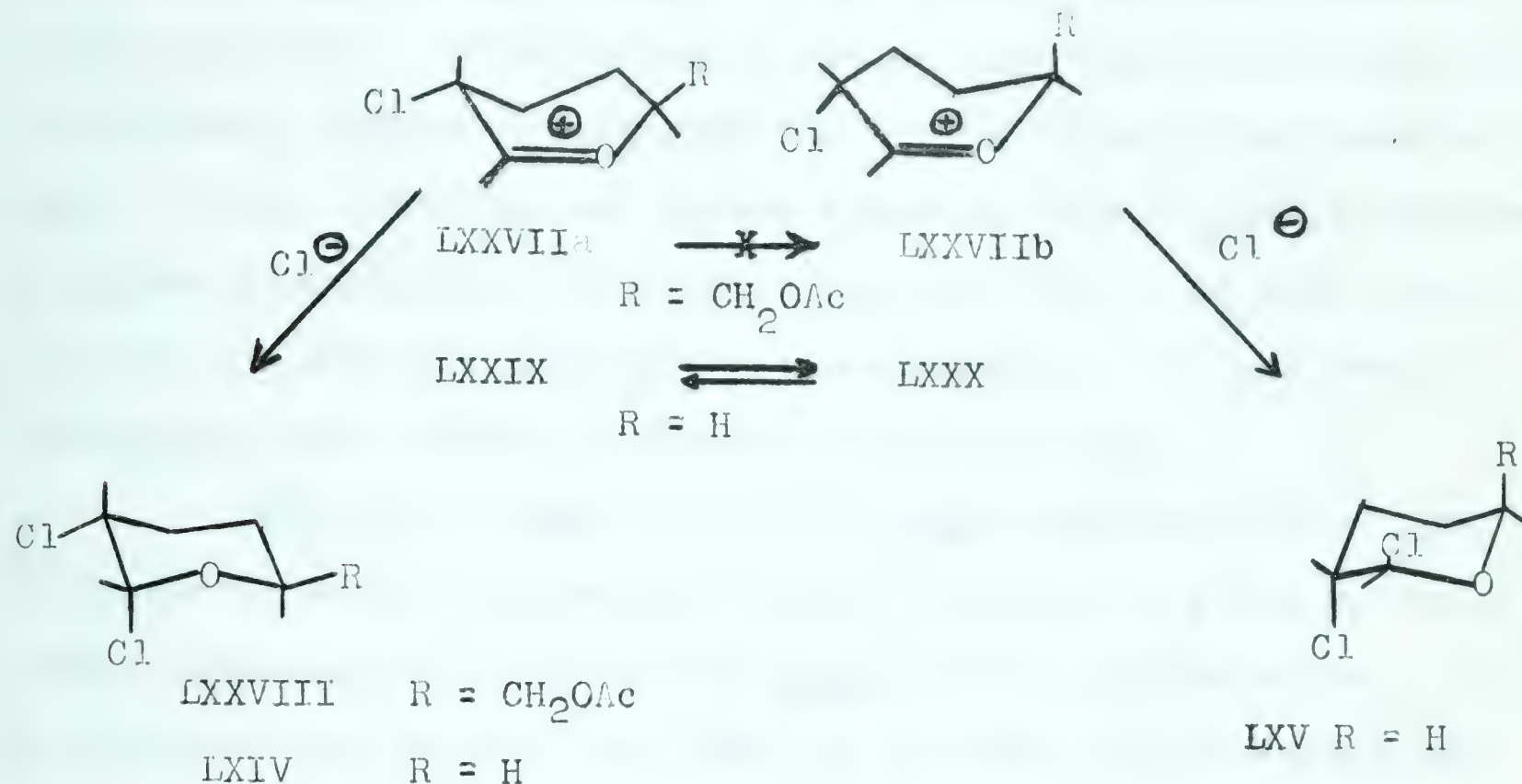
The course of iodination of cholestan-7-one is not known since these workers (148) found that iodination using molecular iodine in tetrahydrofuran (164) was unsuccessful. A comparison with the iodomethoxylation of D-galactal triacetate is therefore not possible. However, it is significant that the axial 2-iodo adduct LVI was produced in 81 per cent yield.

Thus, the conclusion of Miss Castle that "the relative importance of steric and stereoelectronic factors is different for different halogens" is apt, and the experimental results of the work presented in this Thesis strongly suggest that the reactive intermediates for the various halogens are also different. In the light of this observation, a set of generalized rules covering the reactions of all halogens will necessarily involve several parameters. It is of interest to note that the oxygen atom of the enol intermediates derived from the cholestanones XVII and XVIII (page 13) and the lactol-ring oxygen of the glycals, bear a comparable relationship to the double bonds in the respective species. It is therefore probable that the arguments presented above may have some relevance with regard to the  $\alpha$ -halogenation of ketones.

The anchoring effect of the substituent groups on the pyranose ring of sugars and the restrictions to the anomeric effect arising therefrom were discussed in the Introduction. It was seen that with the D-hexoses, an incoming nucleophile could attack only from the alpha side of the molecule in order for both the steric preference of the stable conformation of the pyranose ring



and the anomeric effect to be brought into joint operation. Thus, the addition of chloride ion to an oxocarbenium ion such as LXXVIIa would lead preferentially to LXXVIII. In the absence of a con-



Scheme 12

formationally rigid ring, the ions LXXIX and LXXX may equilibrate more rapidly than they react with the entering nucleophile. The addition of chloride ion to either side of LXXIX or LXXX is now favorable. The products LXIV and LXV both possess the benefit of the anomeric effect. A gauche interaction between vicinal chlorine atoms is not present in LXV. Thus it is not necessarily surprising that, in contrast with the hexose glycals, chlorination of dihydropyran produced both cis- and trans- adducts (LXIV and LXV respectively) in what appeared to be equal amounts (Fig. 6a).

It is noteworthy that the chlorination of p-dioxene proceeds with considerable cis-addition and treatment of the mixture with thionyl chloride achieves isomerisation to the trans-



form (169). Similarly, reaction of the mixture of dichloropyrans with tetraethylammonium chloride in acetonitrile appeared to convert IXIV to LXV, thereby indicating that the reaction product was not the equilibrium mixture. An accompanying side reaction (presumably the  $\beta$ -elimination of HCl to form 3-chloro-5,6-dihydro-1,4-H-pyran, section E-III) made the latter route rather uneconomical. Since epimerisation of the above described cis-2,3-dichloro p-dioxane could also be achieved thermally (169), the high temperature chlorination of dihydropyran was attempted. This route to the trans-isomer proved to be much more rewarding.

The n.m.r. spectrum of the trans-dichloride (Fig. 17), which was discussed in section E-III, indicates that the molecule exists almost exclusively in the trans-diaxial conformation. This is obviously due to the fact that the anomeric effect favors this conformation as against the trans-diequatorial, and in this connection, it is noteworthy that the preferred conformation of trans-2,3-dichloro-p-dioxane (169) has the chlorines in trans-diaxial orientation.

The production of trans-2,3-dibromotetrahydropyran in 90% yield in the bromination of dihydropyran (Fig. 2c) is in keeping with the discussions advanced in the preceding pages.

The products of halogenomethoxylation of dihydropyran are considered in conjunction with those obtained on methanolysis of the related dihalides on page 85.

The reaction of glycosyl halides with alcohols to give products of substitution was first discovered by Koenigs and Knorr (170) in 1900, and a year later they reported that the reaction could be buffered by the addition of silver carbonate, silver

The first part of the paper discusses the importance of the study and the objectives of the research. It also provides a brief overview of the methodology used in the study. The second part of the paper presents the results of the study and discusses the implications of the findings. The third part of the paper concludes the study and provides some final thoughts on the research.

The study was conducted using a qualitative research design. The data was collected through interviews with participants who were selected through purposive sampling. The interviews were conducted using a semi-structured interview schedule. The data was then analyzed using thematic analysis. The results of the study show that there are several factors that influence the outcome of the study. These factors include the quality of the data, the quality of the analysis, and the quality of the conclusions.

The study has several limitations. First, the sample size was small, which may limit the generalizability of the findings. Second, the study was conducted using a qualitative research design, which may limit the ability to generalize the findings. Third, the study was conducted using a semi-structured interview schedule, which may limit the depth of the data collected. Despite these limitations, the study provides valuable insights into the factors that influence the outcome of the study.

The study has several implications for future research. First, future research should aim to increase the sample size in order to improve the generalizability of the findings. Second, future research should aim to use a quantitative research design in order to improve the ability to generalize the findings. Third, future research should aim to use a structured interview schedule in order to improve the depth of the data collected.

nitrate or pyridine. The course of reaction in some of these glycosyl halides was studied by Rhind Tutt and Vernon (172). These authors note that the course of replacement is dependent upon the steric effect of axial carbon-2 substituents and the shielding effect of the departing halide ion frequently causes the reactions to proceed with predominant inversion even where the kinetics exhibited are  $S_N1$  in character. Thus it appears that the normal course of reaction proceeds with inversion at C-I (173), but the tendency for suitably situated groups to participate in, and therefore direct, the course of the reaction was appreciated at an early date (174-177) and has been thoroughly reviewed (77, 178). Hence, in interpreting the course of the Koenigs-Knorr type methanolysis of the mixture of glucosyl dibromides XXI and XXIII, the possibility of neighbouring halogen participation (72-76) was borne in mind.

The reaction of the cis-dibromide XXIII in methanol containing silver carbonate should proceed - as in the case of tetra-O-acetyl- $\alpha$ -D-glucopyranosyl bromide - with complete inversion of C-I (178, 179). However, the corresponding  $\alpha$ -D-manno-isomer XII possesses the 1,2-trans relationship which is conditional for participation (77). Thus the methyl glycoside produced from it could have either the inverted ( $\beta$ -D) or retained ( $\alpha$ -D) configurations.

General experience with the n.m.r. spectra of methyl glycosides (see Tables I-III) leads to the conclusion that equatorial methoxyl groups of  $\beta$ -D anomers give their resonances in the vicinity of 6.40 tau, while with their axial counterparts, the signal is about 0.15 c.p.s. to higher field, (see Table I). In this way the methanolysis of the mixture of dibromides (XXI and XXIII) was



found to proceed with predominant inversion of the reacting anomeric centres. The alpha anomers whose methoxyl signals were at 6.56 and 6.52 tau were produced in a total of less than 20%. Furthermore, deacetylation and hydrogenolysis of the glycosidic mixture gave a better than 60% yield of methyl 2-deoxy-  $\beta$ -D-glucopyranoside.

The n.m.r. spectrum of the reaction mixture (Fig. 3) clearly indicated a high content of methyl 2-bromo-2-deoxy-  $\beta$ -D-glucopyranoside triacetate, XXV. The spectrum of XXV as well as that for the  $\beta$ -D-manno-isomer (XXVII) are shown in Fig. 4. The assignments shown in the spectrum for compound XXV obviously require the  $\beta$ -D-glucopyranose configuration. The  $\beta$ -D-manno configuration of compound XXVII was apparent from the chemical shifts for the methoxy group and anomeric hydrogen as compared to those shown in Fig. 4c for the  $\alpha$ -D-manno-anomer (XXVIII). The latter compound was the main product of the bromomethoxylation of D-glucal triacetate (Fig. 5). The mannosyl dibromide (XXI) therefore reacted without any appreciable participation of the axial 2-bromine.

As could be anticipated from the results outlined in the preceding paragraph, methanolysis of the 1,2-cis-glucosyl dichloride (XXIX) proceeded with exclusive inversion. The extreme similarity between the n.m.r. spectra of the 2-chloro (Fig. 7a) and 2-bromo (Fig. 4a) analogues, XXX and XXV respectively can be seen from Table I.

As far as the galactose case is concerned, methanolysis of the dibromides XLI and XLII produced a mixture of glycosides which on n.m.r. examination at 60 Mc.p.s. appeared to consist of a  $\beta$ -D and an  $\alpha$ -D-glycoside, XLV and XLIII, with methoxy resonances at 6.42 and 6.58 tau respectively. Higher resolution (Fig. 9a)



however, detected a third glycoside XLVI, whose methoxyl resonance at 6.39 tau characterized it as having the  $\beta$ -D-configuration. The mixture was partially fractionated by reverse phase chromatography and a crystalline specimen obtained thereby (XLV) was shown to have the  $\beta$ -D-galacto configuration. It comprised 50% of the reaction product and since the 1,2-cis-adduct (XII) also comprised 50% of the dibromide mixture, it is evident that its methanolysis proceeded with complete inversion.

On anomerisation with titanium tetrachloride in refluxing chloroform, the  $\beta$ -D-galactoside in the preceding paragraph was partially converted to the  $\alpha$ -D-anomer which gave its methoxy resonance at 6.54 tau (Fig. 9c). The latter was therefore not the same as the alpha-isomer obtained on methanolysis (whose methoxy signal was at 6.58 tau); collaterally, the  $\alpha$ -isomer from methanolysis must have the  $\alpha$ -D-talo-configuration. The latter was obtained in a pure state from the chromatogram, and its n.m.r. spectrum shown in Fig. 10 and discussed in section D-I supports its characterization.

The methanolysis of the  $\alpha$ -D-talopyranosyl bromide (XLII) therefore proceeded with some participation of the axial 2-bromine and the products of retention and inversion XLIII and XLVI, respectively, were obtained in about equal amounts (23 and 27%, respectively).

As was expected, the cis- $\alpha$ -D-galactosyl-dichloride XLIX methanolysed with complete inversion, giving the  $\beta$ -D-galactoside (L) as the sole product.

As with the parent dihalides, attempts to fractionate the isomeric mixtures of the 3-halogeno-2-methoxytetrahydropyrans by



distillation did not succeed, and efforts at vapour phase chromatography were equally unavailing. However, as again with the dihalides, the assignment of configuration is facilitated, since the products must be one or other of the two structures shown in Plate III, or their mirror images. Assistance in interpreting the spectra of the mixture of 3-halogeno-2-methoxytetrahydropyrans should be gained from the iodomethoxylation case, and hence this will be reviewed first.

The theoretical considerations of the preceding paragraphs point to the conclusion that iodomethoxylation of dihydropyran should produce an excess of the trans-iodomethoxide LXVIII. In fact, the material obtained on direct iodomethoxylation of dihydropyran implied the presence of only one configurational isomer, since the low field n.m.r. spectrum (Fig. 15c) contained only one signal assignable to the 2-hydrogen at 5.48 tau; and the associated coupling constant ( $J_{23}$ ) of 5.0 c.p.s. is much larger than that expected for hydrogens in gauche equatorial-axial relationship (128). If the values for axial-axial (10.2 c.p.s.) and equatorial-equatorial (2.04 c.p.s.) couplings are assumed (128) then the trans-diaxial and trans-diequatorial conformers of the iodomethoxide (LXVIII) are present in the ratio of 5:3 in the reaction product.

The effect of changing the substituent halogen in the compounds of related configuration is not expected to affect dramatically the chemical shifts of the 2-hydrogen. Experience with the 1,2-trans-halogenomethoxy analogues of the sugar series indicates that changing of the halogen substituent along the series iodine, bromine, chlorine causes the vicinal proton ( $H_2$  of the tetrahydropyrans or  $H_1$  of the sugars) to be shifted by a small but definite



amount (0.09 - 0.18 c.p.s.) to higher field.\* It was therefore expected that in the trans-3-bromo and -3-chloro analogues (LXIII and LXVII) the corresponding signals would occur at slightly higher field. As will be seen below, this turned out to be the case.

"Direct" bromomethoxylation gave a mixture of two isomeric 3-bromo-2-methoxy tetrahydropyrans whose signals for the 2-hydrogens were overlapping at 60 Mc.p.s. Resolution at 100 Mc.p.s. (Fig. 15a) showed that for the component comprising 90% of the reaction product, LXIII, the 2-hydrogen was located at 5.54 tau ( $J_{23} = 4.0$  c.p.s.). For this reason it was assigned the trans-configuration, and the minor component LXII whose 2-hydrogen was at 5.45 tau ( $J_{23} = 2.73$  c.p.s.) was assigned as the cis-isomer.

Similarly, with "direct" chloromethoxylation (Fig. 15b) the component produced in 75% yield (LXVII) gave its signal for  $H_2$  at 5.57 tau ( $J_{23} = 4.0$  c.p.s.) while in the minor (cis) product the signal was at 5.42 tau ( $J_{23} = 3.0$  c.p.s.).

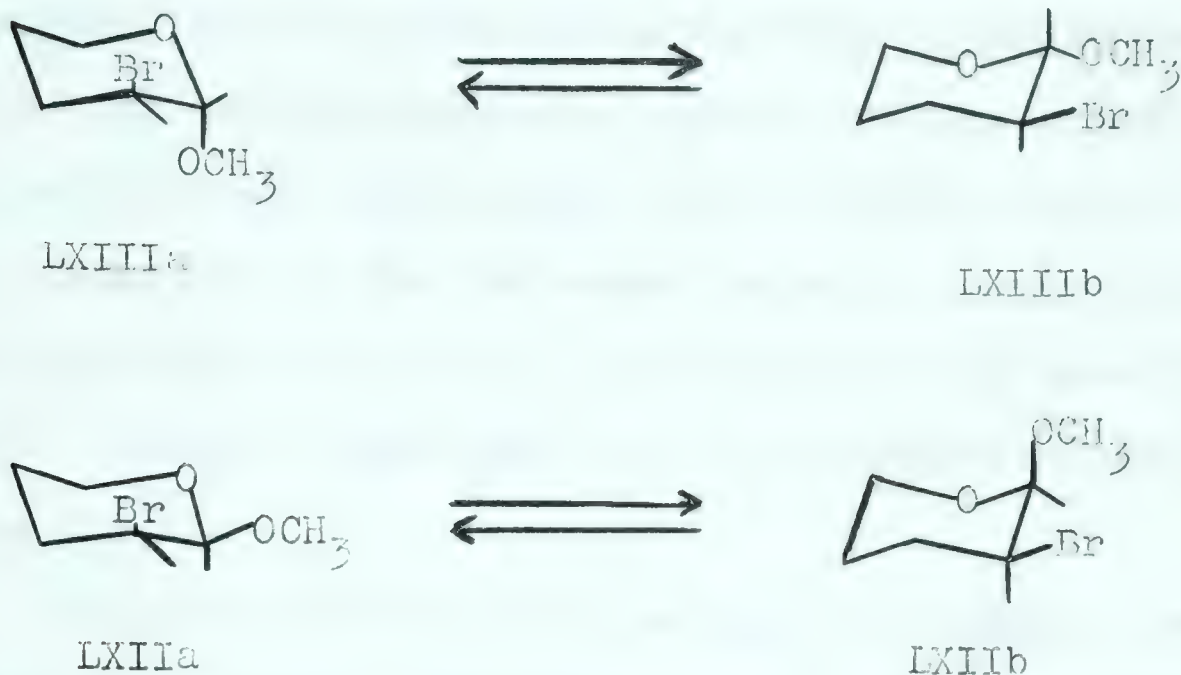
Confirmation for the assignments detailed above was based on the observation (128) that with 1,2-trans-cyclohexene dihalides, the diequatorial conformer tended to predominate (over the trans-diaxial) in polar media. It was therefore surmised that if the n.m.r. spectrum of the above mixture of bromomethoxides was taken in acetonitrile containing tetra-N-ethylammonium bromide, the population of LXIIIb should increase over LXIIIa. Since in this conformer  $H_2$  and  $H_3$  are in trans-diaxial relationship, a

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\* For example, the chemical shift for the anomeric proton of the methyl 2-deoxy-2-halogeno-triacetates of  $\beta$ -D-glucofuranosides,  $\beta$ -D-galactofuranosides or  $\alpha$ -D-mannofuranosides does not differ within each glucose series by more than 0.15 c.p.s. (see Tables I and II)



consummate increase in the coupling constant ( $J_{23}$ ) for the trans-



isomer should be observed. Alteration in the population of LXII (a) and LXII (b) should have little effect on the n.m.r. appearance of the cis-derivative since the coupling constant of the 2 and 3 protons in both conformers is virtually the same (128). Furthermore, it is to be noted that halide ions have a tendency to complex with the three axial protons of structures such as LXXIIIb (180). The effect of this complexing action would also serve to increase the population of LXXIIIb over LXXIIIa.

When the n.m.r. spectrum of the mixture of bromomethoxides was measured in a polar medium (Fig. 14b), the coupling constant of the major component LXIII increased from 3.90 c.p.s. (the value for the neat liquid) to 5.5 c.p.s. while that of the minor component LXII remained unchanged.

An effort was made to establish a chemical proof for these assignments on the basis that trans-elimination of hydrogen



bromide should proceed more readily from the conformer LXII (b) than from LXIII (a). Consequently the cis-bromomethoxide should disappear from the reaction medium at a faster rate than the trans-bromomethoxide. However, this objective was not achieved by any of the systems (sodium methoxide in methanol, piperidine in acetonitrile, or tetra-N-ethylammonium bromide in acetonitrile) used; when the reaction was interrupted after several periods of time, the n.m.r. spectrum of the recovered material showed that the signals for the 2-hydrogens of LXII and LXIII were in the same ratio as at the start. Similar experiments on the chloromethoxides were equally unavailing.

Reaction of the mixture of cis- and trans- dichlorotetrahydropyrans in methanol containing silver carbonate produced equal amounts of the chloromethoxides, LXVII and LXV (Fig. 14). However, similar methanolysis of the trans-2,3-dichlorotetrahydropyran gave 70 per cent of the cis-chloromethoxide; predominant inversion must therefore have occurred during methanolysis of the trans-dichloride. By way of contrast the dibromotetrahydropyrans (which contained 90 per cent of the trans-isomer) gave 58 per cent of the trans-bromomethoxide LXIII (Fig. 17a). Evidently the axial 2-bromine must have participated somewhat so that the methanolysis proceeded with predominant retention.

In the n.m.r. spectra for methyl 2-deoxy-2-chloro (XXXII) and 2-bromo (XXVIII)  $\alpha$ -D-mannopyranoside triacetates (Figs. 7c and 4c respectively, and Table II),  $H_3$  and  $H_4$  both occur between 4.5 and 4.9 tau and are more deshielded than their equatorial anomeric protons. However, with the 2-iodo counterparts (Figs. 8b and 8c),  $H_3$  is at much higher field (5.37 tau). A similar anomaly occurs



in the  $\alpha$ -D-talopyranose series (Table II); in the 2-chloro and 2-bromo derivatives (LII and XLIII respectively) the 3- and 4-hydrogens occur between 4.3 and 4.8 tau. In the 2-iodo-taloside (LVI) however, H<sub>3</sub> occurs at 5.13 tau. It therefore appears that the axial 2-iodine confers a long range shielding effect upon the neighboring axial 3-hydrogen. The reasons for this anomaly are not immediately apparent.



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PART II

The Brominolysis of Carbohydrate  
Iodides



## INTRODUCTION

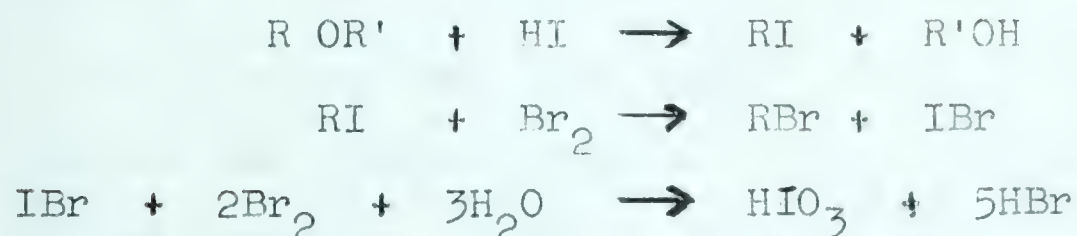
In Part I of this Thesis, the preparation from 3,4,6-tri-O-acetyl-D-glucal of methyl 2-deoxy-2-halogeno-3,4,6-tri-O-acetyl glucopyranosides having the  $\beta$ -D-gluco and the  $\alpha$ -D-manno configurations was described. The  $\alpha$ -D-manno isomer was found in all cases to constitute about 60% of the product, and its predominance was enhanced to 80% on adding to the reaction mixture a molar excess of S-collidine. The possibility of replacing the halogen by various nucleophilic species seemed a promising route for achieving new syntheses of several sugars (e.g. glucosamine with amide ion as nucleophile). The iodine of the 2-iodo-glycosides should be most susceptible to displacement; however, it proved so highly resistant to nucleophilic attack on the carbon, that only elimination was obtained under a variety of solvolytic conditions (1).

Since the iodine could not be "pushed" off, attempts were made to "pull" it off. The latter approach necessitates abstracting electrons directly from the iodine, for which an oxidizing agent is required. However, both lead tetraacetate and sodium periodate left the molecule virtually unaffected. It was decided to examine the dark reaction of the iodide with bromine under the standard Viebock-Ziesel conditions (2) used in alkoxyl group determinations in which alkyl ethers are cleaved with hydrogen iodide to yield an alkyl iodide. The latter now reacts in the dark with bromine in glacial acetic acid, N in potassium acetate. In view of the relatively high concentration of acetate ion and polarity of the medium, it could be expected that the inversion mechanism would lead to replacement of the axial iodine atom by



acetoxy group. The rate of the cleavage of the carbon-iodine bond could be conveniently followed by titration of the iodate content after various periods of time. Since this reaction was to form the basis of the research presented in this Thesis, its history will be briefly reviewed.

The earliest method of determining alkoxyl groups quantitatively is the gravimetric procedure of Ziesel (3) in which the O-alkyl bond is cleaved with hydrogen iodide, and the resulting alkyl iodide converted to silver iodide by alcoholic silver nitrate. In an effort to improve this tedious method, the alkyl iodide was distilled (2,3) into a receiver containing bromine in acetic acid suitably buffered with alkali acetate. It was soon discovered (2) that the alkyl iodide was rapidly decomposed with formation of alkyl bromide and iodine bromide. The latter was subsequently oxidized by the bromine to iodate, (Scheme 1) and thus standard iodometric titration with sodium thiosulphate formed the basis for quantitative analysis (4). Similar reaction had hitherto been



Scheme 1

known, for Rae (5) had observed that ammonium iodide, when exposed to bromine vapour, gave  $\text{NH}_4\text{BrIBr}$  as a red solid. The instability of these iodoso dihalides and their facile conversion to iodate found analogy in the brominolysis of potassium iodide (6) which was thought (7) to proceed through similar stages.

The displacement of iodine at a saturated carbon by the



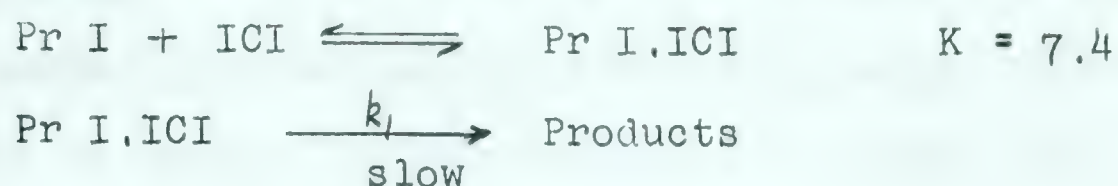
agency of molecular halogens of the type  $X_2$  or  $IX$  in radical (8-10) and non-radical (11-15) reactions had been known for several years prior to Viebock's work. The reaction was discovered by Geuther (16) and, in 1865, Freidel (17) observed that addition of bromine to isopropyl iodide led to the formation of isopropyl bromide and propylene dibromide, iodine being liberated in the process. Recently the conversion of the same substrate to propylene chloriodide and isopropyl chloride by iodine monochloride was described by Keefer and Andrews (12).

It has been known that tervalent iodine forms compounds of the type  $RIX_2$  ever since Willgerodt (18) isolated phenyl iodoso dichloride by the action of chlorine on phenyl iodide. The ammonium iodoso dibromide obtained by Rae (5) belongs to this category. On reacting the phenyl iodoso oxide obtained by base hydrolysis of the dichloride with appropriate acids, several iodoso salts were obtained (19). Although no iodoso dibromides appear to have been isolated (19), Viebock postulated their intermediacy in the above-mentioned brominolysis of isopropyl iodide. In fact iodoso dihalides appear to have appreciable stability only in the aromatic series. Their analogues in the aliphatic series have been isolated only at exceedingly low temperatures, (11, 20) although spectroscopic (11) and kinetic (12) data indicates that at room temperature this 1:1 complex of iodide and halogen exists to a considerable degree in solution. Thus, the stabilities of the iodine dihalide salts are reminiscent of those for aromatic and aliphatic diazonium salts and, as will be seen below, their reaction properties are very similar.

For the reaction of isopropyl iodide and iodine chloride,



Keefer and Andrews (12) established the following sequence to



### Scheme 2

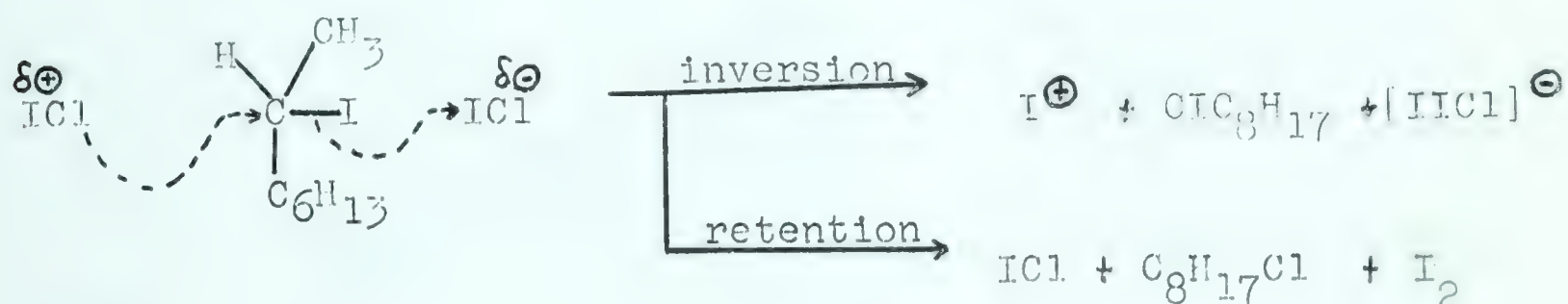
account for the observations that (i) the rate does not depend directly on the concentration of isopropyl iodide and (ii) certain absorptions in the ultraviolet spectrum are attributable only to the existence of such complexes. The speculation by earlier workers (4,20) regarding such possible intermediates is, therefore, justifiable.

The stereochemistry and mechanism of the halogenolysis reaction of alkyl iodides has received considerable attention. The reaction of optically active 2-octyl iodide with bromine at low temperatures (15) gives mainly the inverted product. At higher temperatures the stereoselectivity is lost and, in addition, considerable dihalide is formed. Corey and Wechter (14) examined the extent of inversion in the reaction of optically active 2-octyl iodide with chlorine and iodine chloride in a number of solvents. The 2-octyl chloride formed was isolated by distillation in 30 to 50% yield and its rotation was measured under standard conditions. The extent of inversion with chlorine as the reagent was 1.5 to 2.3 times greater than retention when inert, non-polar solvents were used (methylene chloride, ether, pentane and ethyl acetate). The highest degree of inversion (10.25 times greater) occurred when a 3:1 mixture of methylene chloride and methanol 4M in hydrogen chloride was used. In the absence of the hydrogen chloride, the extent of inversion was reduced to 5.8 times that

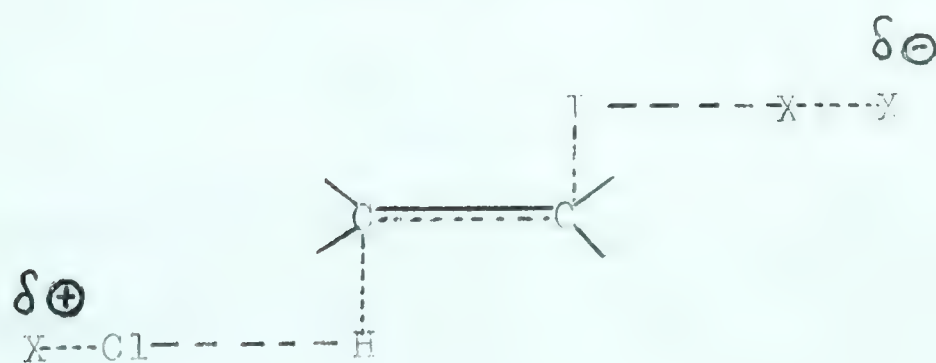


of retention. In the presence of methanol, methyl 2-octyl ether was also formed.

Keefer and Andrews (12,13) have examined the kinetics of the reaction in carbon tetrachloride and concluded that the rate-controlling step involves attack by the halogen on the 1:1 complex (4,11) of the alkyl iodide and the halogen. The experimental data have been interpreted in terms of a termolecular mechanism, Scheme 3a, because on going from chlorine to iodine monochloride, the ratio  $k_{\text{inversion}}/k_{\text{retention}}$  was found to increase. This was



Scheme 3a

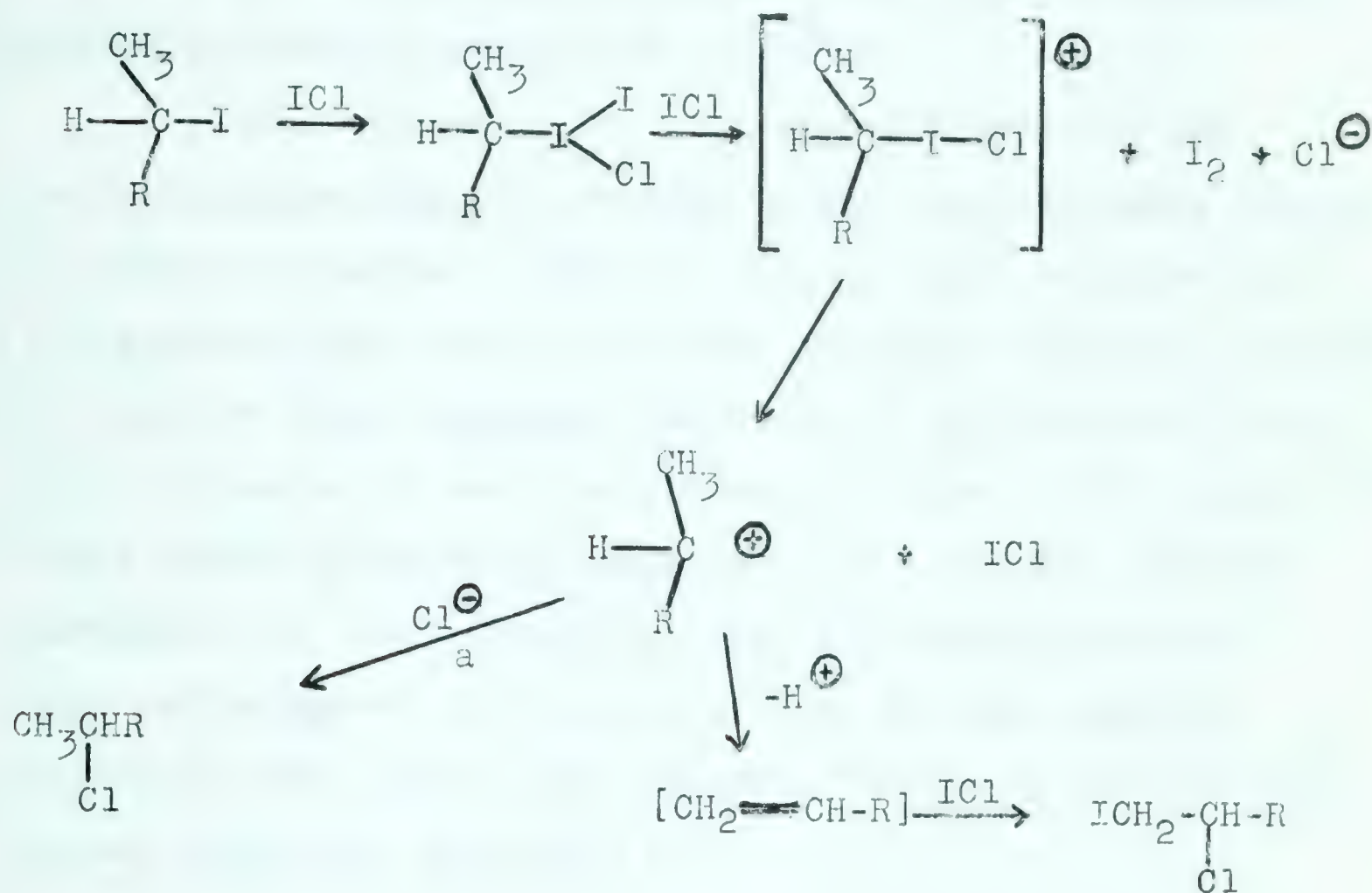


Scheme 3b

attributed to the greater nucleophilicity of chlorine in iodine monochloride than in chlorine. However, while a termolecular mechanism can account for the halogen replacement at the reaction site, it offers no explanation for the production of dihalides during the reaction. The latter, which are formed in accordance with the Saytzeff rule (15), undoubtedly arise from olefins; a termolecular transition state leading to an olefin is implausible



since the developing charges would have to be distributed over six bonds (Scheme 3b ). (It is noteworthy that Corey (14) did not report the formation of any dihalides).



Scheme 4

An alternative view was offered by Keefer and Andrews (13) who suggested that a second molecule of halogen may make an electrophilic attack on a halogen of the complex (Scheme 4). Thus, the formation of a high energy alkyl iodonium halide cation can be envisaged which presumably could rapidly decompose to a carbonium ion-iodine halide molecule pair. Attack on the ion by a nucleophile from the immediate environment could then account for the products of replacement. Increased solvent polarity would be expected to facilitate separation of the carbonium ion-iodine halide pair and the neighboring halide anion, and thus account for



the increase in inversion noted with increasing polarity of the solvent (14). The departing iodine halide would be expected to help shield the carbonium ion from nucleophilic attack to produce products of retention.

The formation of a high energy alkyl dihalide cationic intermediate is favored by the indiscriminate courses of reaction observed. First of all, it is to be noted that the substitution reaction is often the minor reaction. Instead, elimination (and subsequent formation of the dihalide) can be the main course of reaction (Scheme 4), even in the absence of added proton abstracting reagents (17). Also in line with carbonium ion formation is the fact that Wagner-Meerwein type rearrangement of the neopentyl to the sec.-isobutyl carbon skeleton occurs when neopentyl iodide is treated with either bromine or chlorine (15).



## EXPERIMENTAL

### A. Methods and Materials

#### I. Methods

Unless otherwise stated, the methods used were the same as those described in Section A of Part I of this Thesis.

#### II. Materials

The exploratory reactions described in Section B were performed on the reaction product obtained from iodomethoxylation of D-glucal triacetate (Part I; C-V) containing the  $\beta$ -D-glucoside (34%) and the  $\alpha$ -D-mannoside (66%) isomers of methyl 2-deoxy-2-iodo-pyranoside triacetates.

### B. Exploratory Reactions

#### I. Lead Tetraacetate

To a solution containing 10 g (23.3 mM) of lead tetraacetate in 100 ml of acetic acid, 1.47 g (3.4 mM) of the mixture of 2-iodo-glycosides was added. The solution was heated on a constant temperature bath at 75° and after 24 hours, it was poured into water and extracted with chloroform. The dried chloroform layer afforded 1.35 g of material which was shown by n.m.r. to be virtually unchanged from the starting material.

#### II. Bromine

The conditions for Zeisel methoxyl determination as prescribed by Viebock and Schwappach (2) were used in the preliminary experiments, and reagent grade methyl iodide was used for control purposes.

100 ml of a solution containing 32 g (200 mM) of bromine in 10% potassium acetate in freshly distilled acetic acid was prepared. The solution was equally divided into two 100 ml



volumetric flasks, and to one, 2.15 g (5 mM) of the mixture of 2-iodoglycosides was added. To the other, 0.71 g (5 mM) of methyl iodide was added, and each mixture was then diluted with the buffer solution to 100 ml. From time to time, 10 ml aliquots of each solution were pipetted into 25 ml of aqueous sodium acetate and formic acid was added dropwise with swirling until the excess bromine had been reduced (4). The solution was acidified with 10 ml of 2N sulphuric acid, and after adding 10 ml of 10% potassium iodide solution, the liberated iodine was titrated with 0.1 N sodium thiosulphate solution (see Table I).

Time	Control	Sample	Percent completion
	(volume 0.1 N Thiosulphate)		sample/control
1 hour	30.5	0.5	1.6
24 hours	30.1	0.8	2.7
52 "	29.7	1.0	3.3
72 "	-	1.2	4.0
96 "	-	2.2	7.3
1 week	-	3.6	11.6

Table I

### Reaction of 2-Iodoglycosides with Bromine

When 10 ml of the initial reaction mixture in 2(a) was heated at 75° for 24 hours, it consumed 11.4 ml of the thiosulphate solution indicating 37% reaction.

### III. Bromine and Silver Acetate

1. A solution of the 2-iodo-glycosides in the potassium acetate-bromine-acetic acid mixture similar to that used in section B-II



was prepared.

Aliquots (10 ml) of the solution were pipetted into six 100 ml Erleymeyer flasks and 0.55 g (3.3 mM) of silver acetate was added to each. The flasks were protected from light by wrapping with aluminum foil, shaken and analyzed at the indicated time intervals in the following manner. A 25 ml portion of 25% aqueous sodium acetate was added to each flask and the bromine was destroyed by dropwise addition of formic acid. The silver salts were then removed and the filtrate was prepared for titration as described in B-II. The results are shown in Table III.

Time	Vol. 0.1N Thiosulphate	Percent completion (based on theoretical consumption of thio- sulphate)
0.5 hours	9.6	32.0
5 "	16.9	56.5
12 "	17.1	57.1

Table II

Reaction of 2-iodo-glycosides with Bromine and Silver Acetate

2. Since the reaction in B-III1 had evidently ceased, a further 0.55 g of silver acetate was added to one of the remaining flasks to raise its concentration to 6.6 mM.

3. To another flask, 1.10 g of silver acetate was added in order to make its concentration equimolar with the bromine.

Both flasks in B-III2 and B-III3 were shaken for 12 hours and the solutions were analyzed as in B-III1. The mixture from B-III2 consumed 29.6 ml of 0.1N thiosulphate and that from B-III3 28.9 ml, indicating 97 and 94.5% reaction respectively. The conditions in B-III2 were therefore adopted since the additional



silver acetate in B-III 3 had no beneficial effect. The silver precipitate was shown by standard qualitative techniques to be silver bromide (21).

### C. Brominolysis of Iodides

#### I. Analytical Reactions

For studying the rates of these reactions, pure specimens of each of the 2-iodo sugars (XXXVI and XXXVIII in Part I) were used.

Six flasks, each containing 10 mM of bromine, 6.6 mM of silver acetate and 0.5 mM of the 2-iodo glycoside in 10 ml of the potassium acetate buffer were shaken in the dark. At intervals these were analyzed as in B-III. The results plotted in Fig. 1 indicate little differences in the reactivity of the sugars. For this reason, a reaction period of 7 hours was adopted for these brominolyses.

#### II. A Typical Preparative Reaction

The reaction conditions developed in B-III were adopted. 3.24 g (7.5 mM) of the mixture of 2-iodo-glycosides was dissolved in 150 ml of a 10% solution of potassium acetate in acetic acid which contained 24.0 g (150 mM) of bromine. Silver acetate, 16.7 g (100 mM) was added and the reaction mixture was stirred in the dark. After a seven hour reaction time, 150 ml of a 25% aqueous solution of sodium acetate was added and the bromine was reduced by the addition of formic acid. The product was isolated by filtration to remove insoluble salts and the filtrate was extracted repeatedly with chloroform. The extracts were washed to neutrality with saturated sodium bicarbonate solution and with sodium thiosulphate solution to remove traces of iodine.



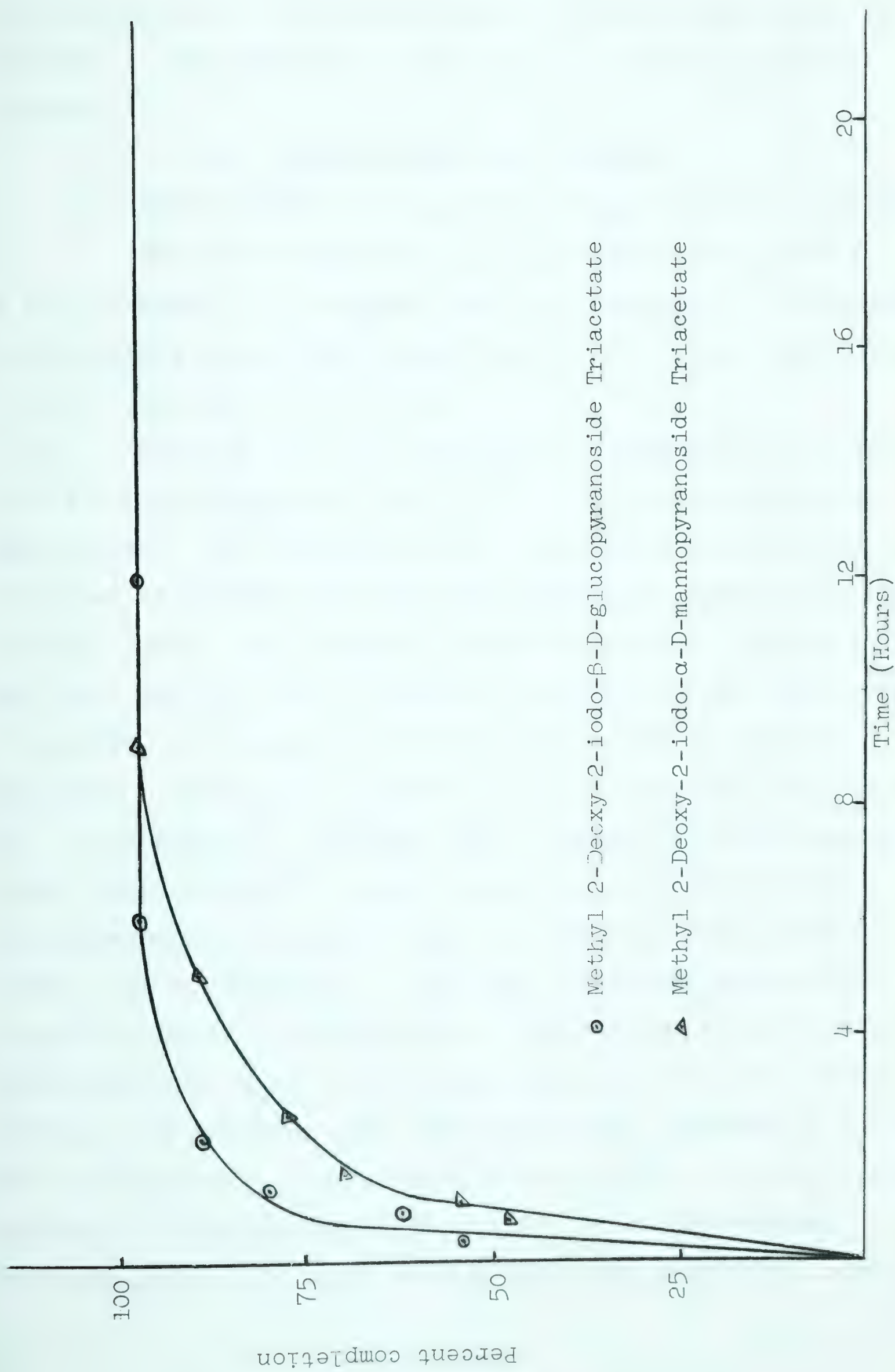


Fig. 1

Rates of Brominolysis of 2-iodoglycosides



The chloroform layer was then dried by passage through chloroform-wetted paper. On evaporation, 2.4 g of a brown syrup was obtained. This material is referred to in section C-III as "Product I".

### III. Products from Model Iodides

#### 1. From Methyl 6-Deoxy-6-iodo- $\alpha$ -D-glucopyranoside Triacetate.

The 6-iodo-glycoside (I) [m.p. 148-9°,  $[\alpha]_D$  121° (c, 1 in chloroform)] was prepared starting from methyl  $\alpha$ -D-glucoside by the method of Zief and Hockett (22). Its n.m.r. spectrum is shown in Fig. 2a.

(a) A 215 mg (0.5 mM) sample of I was reacted in the dark with 2.6 mM of bromine in 18.5 ml of 10% potassium acetate in acetic acid. The deiodination was followed titrimetrically as described in section B-III and was complete in seven hours. The product, 163 mg, was isolated in the usual manner (section C-II) and was found by n.m.r. to comprise a mixture of two components II and III. A solution of the product in ethanol readily deposited a crystalline compound (II), m.p. 109-111°,  $[\alpha]_D$  144.1 (c, 1 in pyridine). Although these constants are not exactly those reported (23) for methyl 6-bromo-6-deoxy-tri-O-acetyl- $\alpha$ -D-glucopyranoside, the n.m.r. spectrum (Fig. 2b) could leave no doubt as to its identity. The major difference between its spectrum at 60 Mc.p.s. and that for methyl tetra-O-acetyl- $\alpha$ -D-glucopyranoside (III), Fig. 2c, was the chemical shift for the methylenic 6-hydrogens from 5.85 tau for the 6-acetate to 6.0 tau for the 6-bromide. In the case of the 6-iodide (I), the starting material, this signal appeared at 6.72 tau. Furthermore, on hydrogenolysis of 10 mg of II with palladium as catalyst, followed



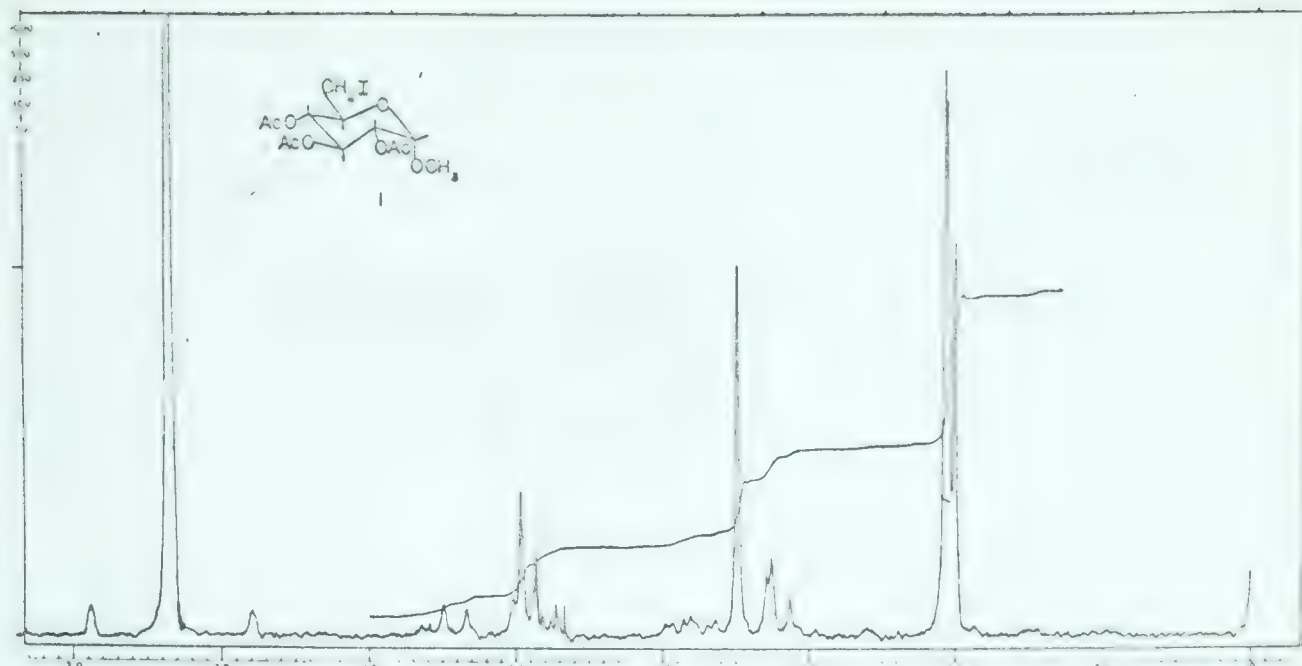


Fig. 2a Methyl 6-Deoxy-6-iodo- $\alpha$ -D-glucopyranoside Triacetate

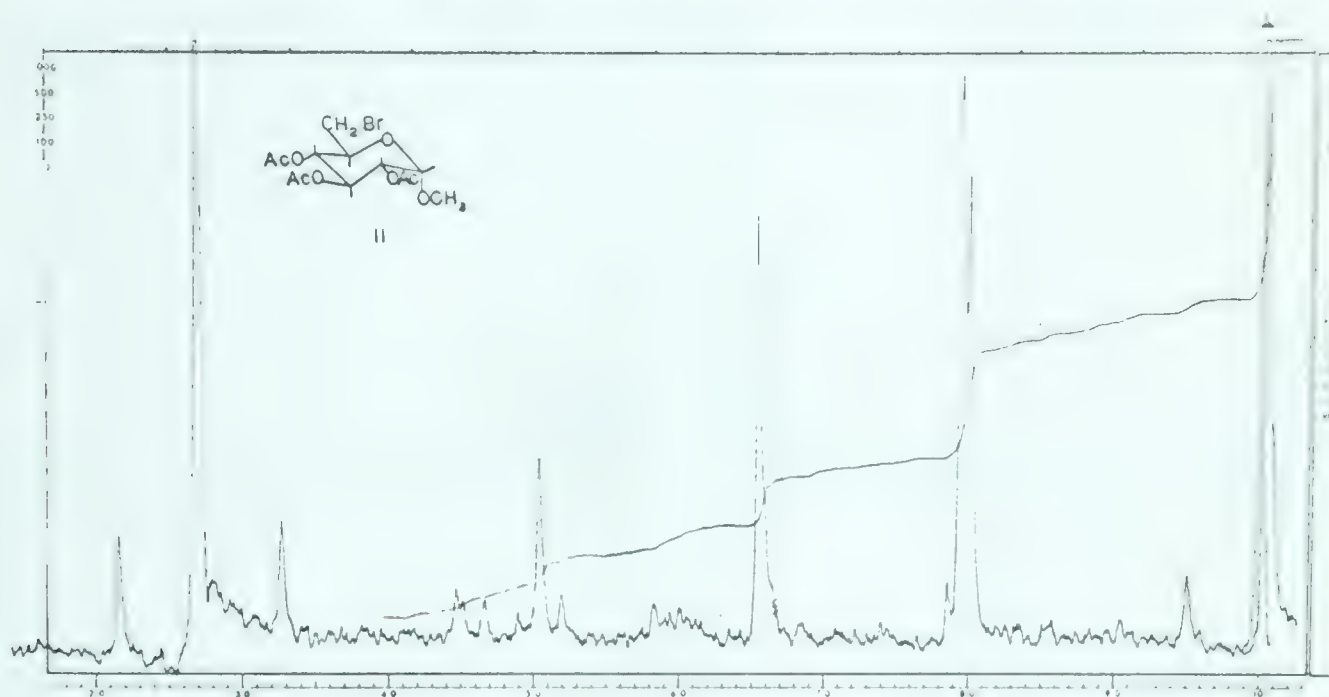


Fig. 2b Methyl 6-Deoxy-6-bromo- $\alpha$ -D-glucopyranoside Triacetate

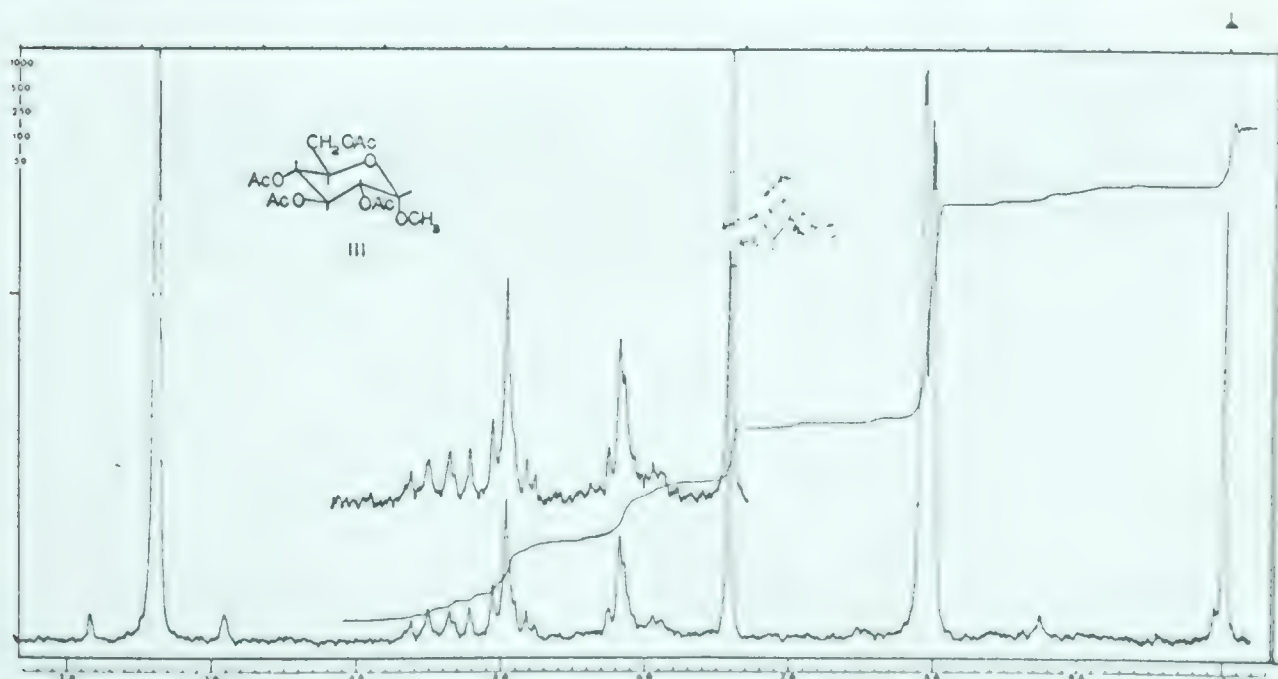


Fig. 2c Methyl  $\alpha$ -D-glucopyranoside Tetraacetate



methoxyl signals at  
100 Mc.p.s. for:

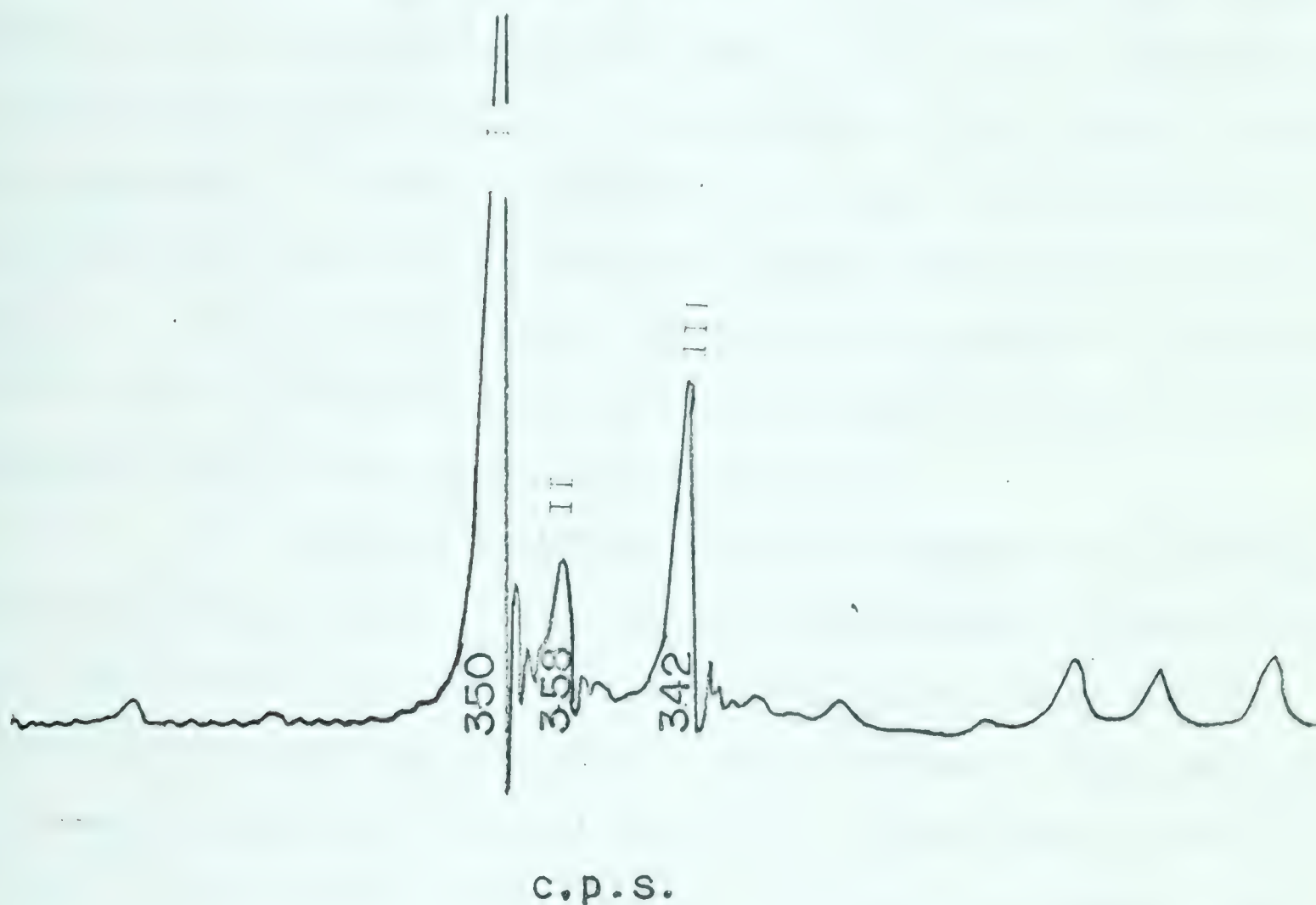


Fig. 3 Methoxyl signals at 100 Mc.p.s. for Methyl 6-Deoxy-6-iodo- $\alpha$ -D-glucopyranoside Triacetate (I), Methyl 6-Bromo-6-deoxy- $\alpha$ -D-glucopyranoside Triacetate (II) and Methyl  $\alpha$ -D-glucopyranoside Tetraacetate (III).



by deacetylation with 5% triethylamine in aqueous methanol (50%), a substance with the same  $R_f$  value as methyl 6-deoxy-  $\alpha$ -D-glucopyranoside was obtained. An authentic sample of the latter was available by hydrogenolysis of the starting material.

The other product formed in the brominolysis was readily isolated by fractional crystallization and found by direct comparison with a specimen from the shelf, to be methyl tetra-O-acetyl- $\alpha$ -D-glucopyranoside (III). The signals for the methoxyl groups in compounds I, II and III occurred at 6.50, 6.52 and 6.58 tau and were well resolved by the spectrometer operating at 100 Mc.p.s., Fig. 3. The relative intensities of these signals in the spectrum of the above described reaction product showed the ratio of 6-bromide (II) to 6-acetate (III) to be 1.1:1

(b) The reaction described above was repeated at ten fold dilution using 185 ml of the 10% potassium acetate in acetic acid. The reaction was only 47% complete after seven hours, and the ratio of II to III was 0.4 to 1. After 43 hours, the reaction was complete and the ratio of II to III in the product was 0.6:1.

(c) In an experiment identical to that described in (b), except that 0.835 g (5 mM) of silver acetate was added, the reaction was complete within three hours, and the product was the pure 6-acetate, III.

(d) When the reaction was performed under conditions identical to those described in section C-II, the ratio of II and III in the product was 0.82:1.

## 2. From Cyclohexyl Iodide

Cyclohexyl iodide, 3.20 g (15 mM), was treated with 100 ml of a 10% w/v solution of potassium acetate in acetic acid



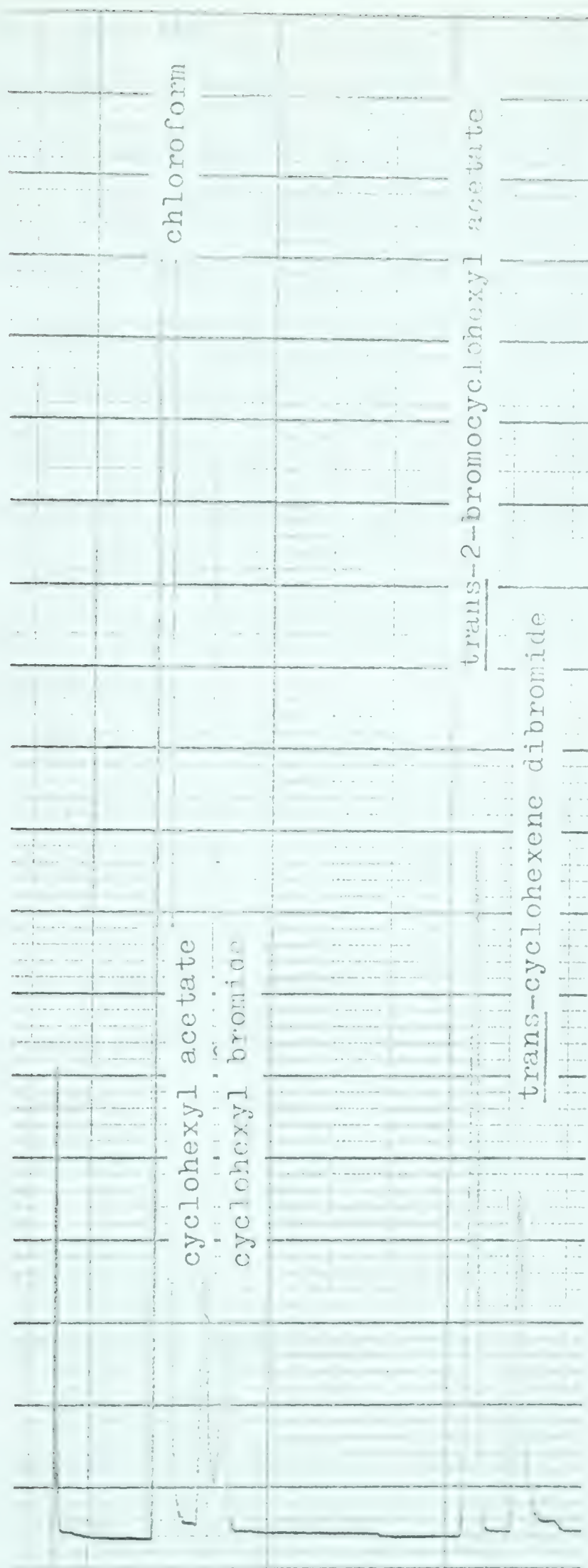


Fig. 4.  
Gas-liquid partition  
chromatogram of the  
product from brominolysis  
of cyclohexyl iodide.



containing 33 g (200 mM) of bromine for seven hours. A 100 ml portion of 25% aqueous sodium acetate was then added, and the reaction product, 2.16 g, was isolated in the usual manner (see section C-II). The oily material was subjected to gas-liquid-partition-chromatography on a silicone oil-celite column using a temperature program over the range 50° to 225°. Four components were detected comprising 4.3, 6.7, 34.4 and 54.6% of the material which passed through the column, Fig. 4. These components were identified by direct comparison of their retention times with those of authentic samples and found to be cyclohexyl bromide, cyclohexyl acetate, trans-cyclohexene dibromide and trans-2-bromocyclohexyl acetate, respectively.

### 3. From Mixture of 2-Iodo-glycosides

The syrupy material from the preparative reaction, described in section C-II as "Product I", gave an n.m.r. spectrum which indicated the presence of a number of methoxyl containing compounds. Profound degradation accompanying deacetylation with methanolic ammonia was deduced from the maze of spots produced on paper chromatograms. "Product I" evidently underwent ammonolysis since ammonia was evolved on heating the deacetylated material with soda lime. In an effort to stabilize the material, 0.3 g of "Product I" was subjected to atmospheric hydrogenation in acetic acid (10 ml) containing Adams<sup>2</sup> catalyst (30 mg). Hydrogenation was complete after 5 hours and catalyst was removed and the filtrate was diluted with water for extraction with chloroform. The recovered product showed extensive material loss (49%) and the n.m.r. spectrum indicated a multitude of degradation products.

"Product I" was obviously labile, both to acids and to



bases; but it was hoped that, under the reductive conditions of sodium borohydride, the degradation would be less severe.

"Product I", 0.382 g, was dissolved in methanol (10 ml) and 0.70 g sodium borohydride added. After 30 minutes, reduction was complete since the solution no longer gave a positive test with Fehling's solution (24), but the mixture was left for 7 hours to achieve deacetylation. An excess of acetic acid was then added and the solution was reduced to dryness. Methanol was evaporated in vacuo several times from the residue to remove the boric acid, and the sodium ion was removed by treating an aqueous solution of the product with sulphonic acid resin in the acid form. The deionized eluate was then evaporated to dryness. Paper chromatography and n.m.r. analysis (in deuterium oxide) of the residue showed that this treatment had caused less degradation than either of the processes described above.

#### D. Brominolysis of Methyl 2-Deoxy-2-iodo-

##### $\beta$ -D-glucopyranoside Triacetate

I. 1,3,4,6-Tetra-O-acetyl-2,5-anhydro-1-methoxy- $\alpha$ -  
and  $\beta$ -D-mannose, (IV $\alpha$  and IV $\beta$ ).

Brominolysis of methyl 2-deoxy-2-iodo- $\beta$ -D-glucopyranoside triacetate (3.24 g) in the manner described in section C-II yielded 2.48 g of material whose n.m.r. spectrum is shown in Fig. 5. Since the preliminary experiments in section C-III had suggested that these compounds were base labile, the material was subjected to reverse phase chromatography (see Part I, section D-I). It was thereby found to contain two major components. After attempted preparative reverse-phase-column chromatography using various irrigation systems (10% ethyl ether in Skellysolve-B, 5 and 10% diisopropyl ether in Skellysolve-B) a 15% solution of diisopropyl



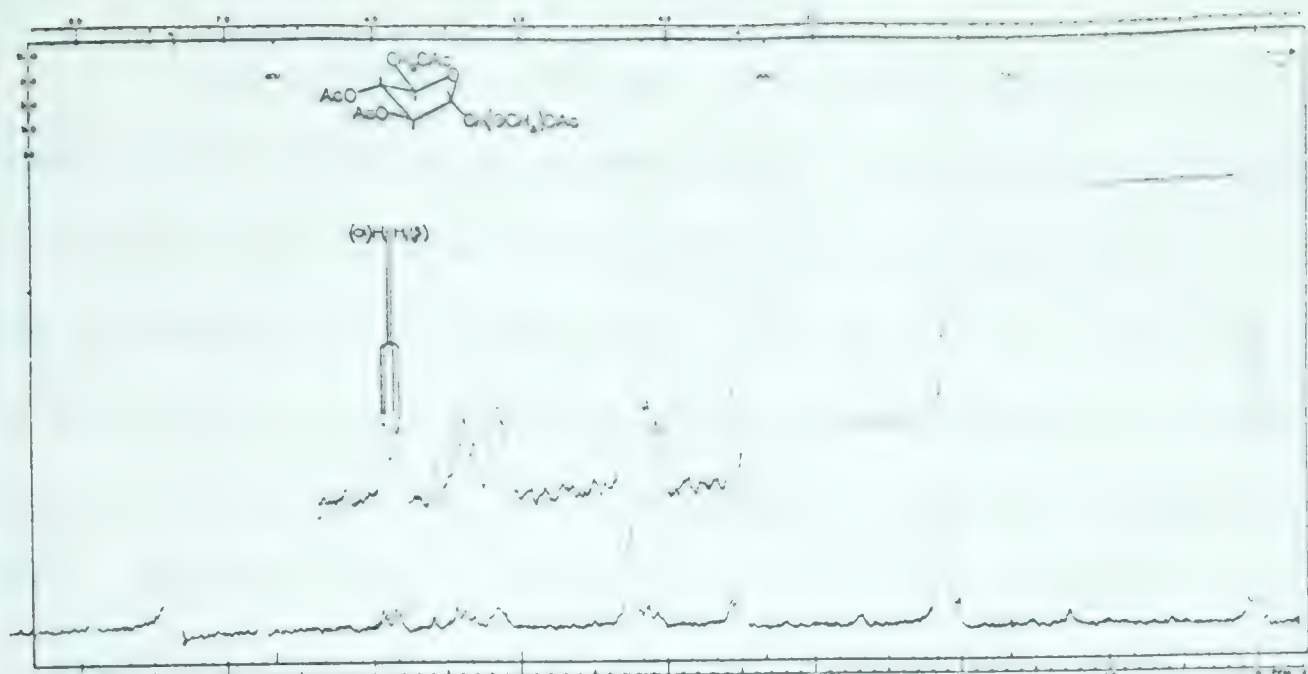


Fig. 5a Products from Brominolysis of Methyl 2-Deoxy-2-iodo- $\beta$ -D-glucopyranoside Triacetate

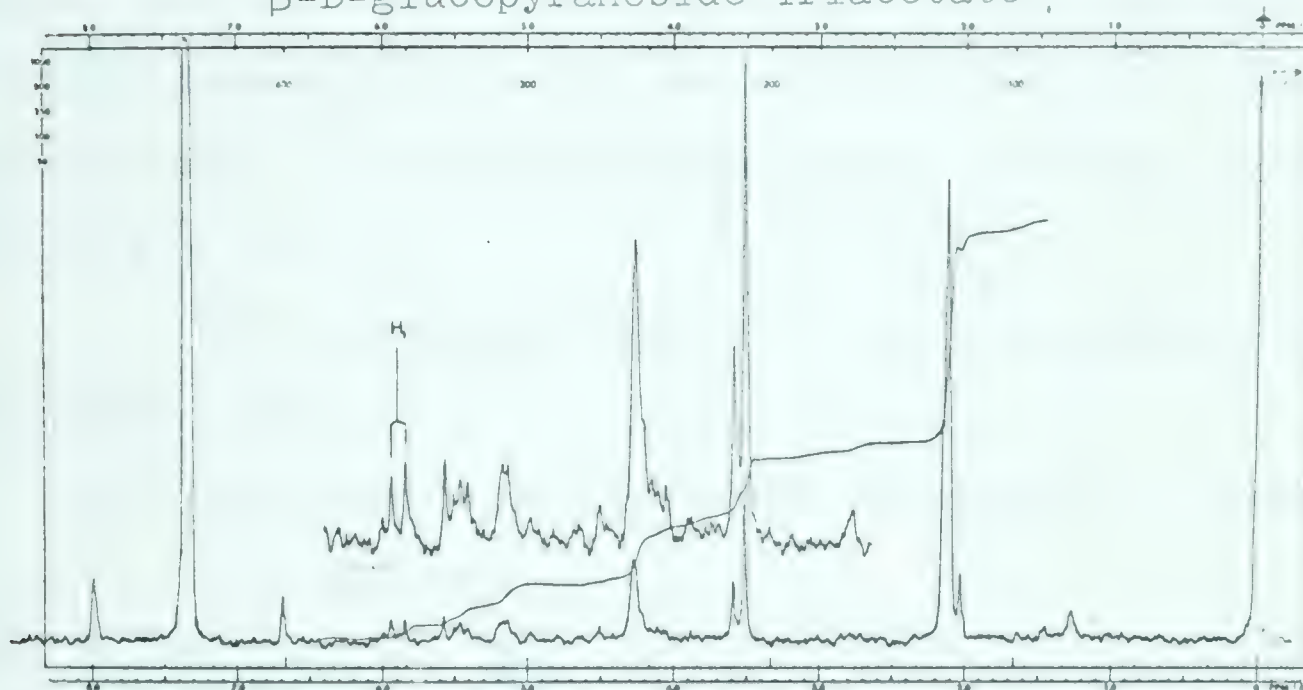


Fig. 5b 1,3,4,6-Tetra-O-acetyl-2,5-anhydro-1-methoxy- $\beta$ -D-mannose

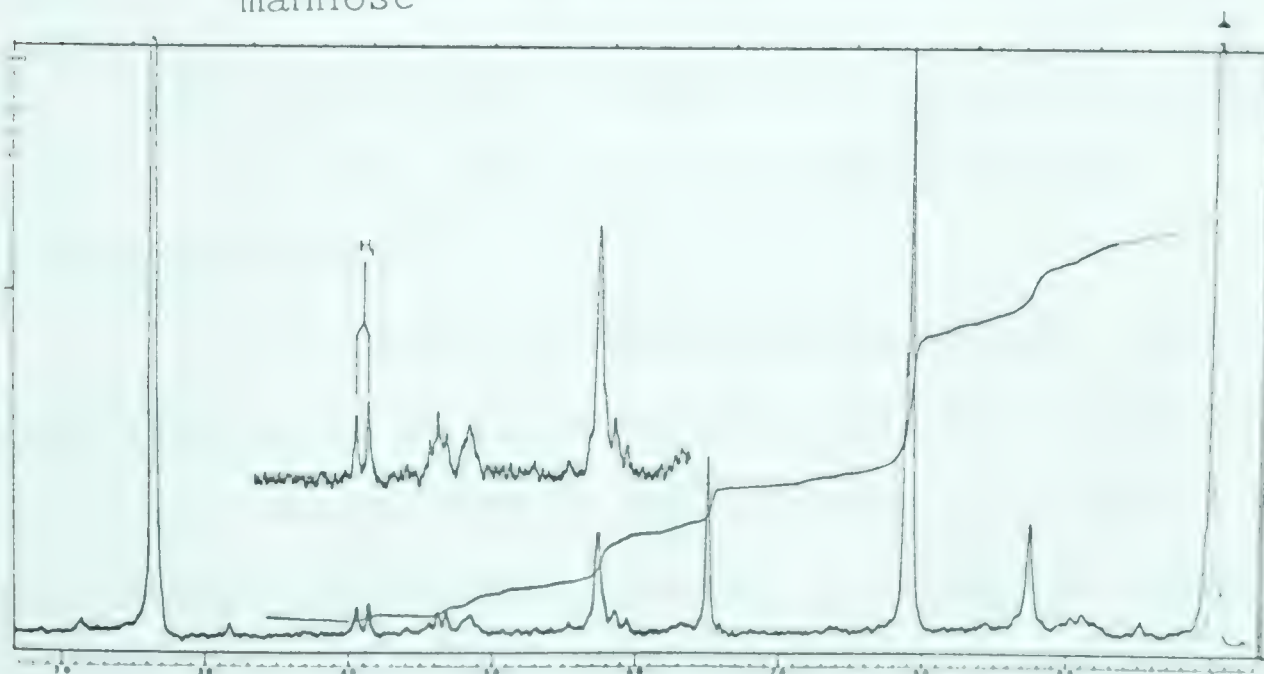


Fig. 5c 1,3,4,6-Tetra-O-acetyl-2,5-anhydro-1-methoxy- $\alpha$ -D-mannose



ether in Skellysolve-B was adopted.

The mixture, 853 mg, was added to a 2.5 cm x 27.5 cm column of silicic acid impregnated with dimethyl sulphoxide and eluted with 15% diisopropyl ether in Skellysolve-B. The first pure component (IV $\beta$ ), 261 mg,  $[\alpha]_D$  46.3° ( $c$ , 2.26 in chloroform) was isolated in the 1500 to 1600 ml fraction of eluate. The next 75 ml provided 350 mg of a mixture of the two components. Compound (IV $\alpha$ ), 161 mg,  $[\alpha]_D$  49.4° ( $c$ , 2.7 in chloroform) was obtained in the following 80 ml of eluate. Both the pure compounds gave n.m.r. spectra, Fig. 5b and 5c respectively, with sharp signals for four acetoxy groups and one methoxy group at 7.88 and 6.49 tau respectively. The spectra were almost identical in the range 6.0 to 4.3 tau.

The overlapping zone from the chromatogram was used for diagnostic tests.

- (a) Lassaigne test indicated the absence of halogen in IV $\alpha$  and IV $\beta$ .
- (b) Methanolic ammonia caused profound degradation.
- (c) Hydrogenation in methanol was without effect.

## II. The Dimethyl Acetal of 2,5-Anhydro-D-mannose (V), and the Triacetate (VI) of V

### 1. Preparation of V

A portion of the brominolysis product 0.410 g was reacted with 15 ml of 2% methanolic hydrogen chloride for 7 hours. The acid was neutralized by the addition of pyridine and the residue after evaporation, 162 mg, was shown by paper chromatography to contain only one component, which gave a strong reaction with



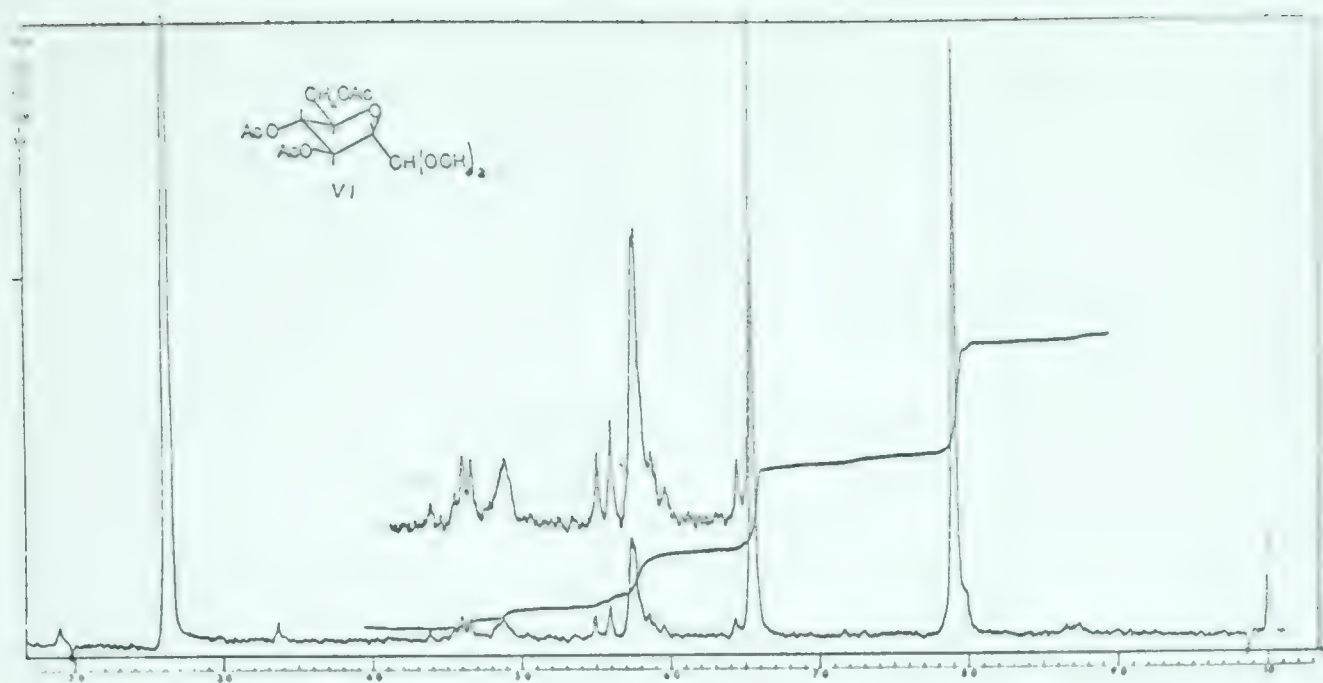


Fig. 6 The Dimethyl Acetal of 2,5-Anhydro-D-mannose Triacetate

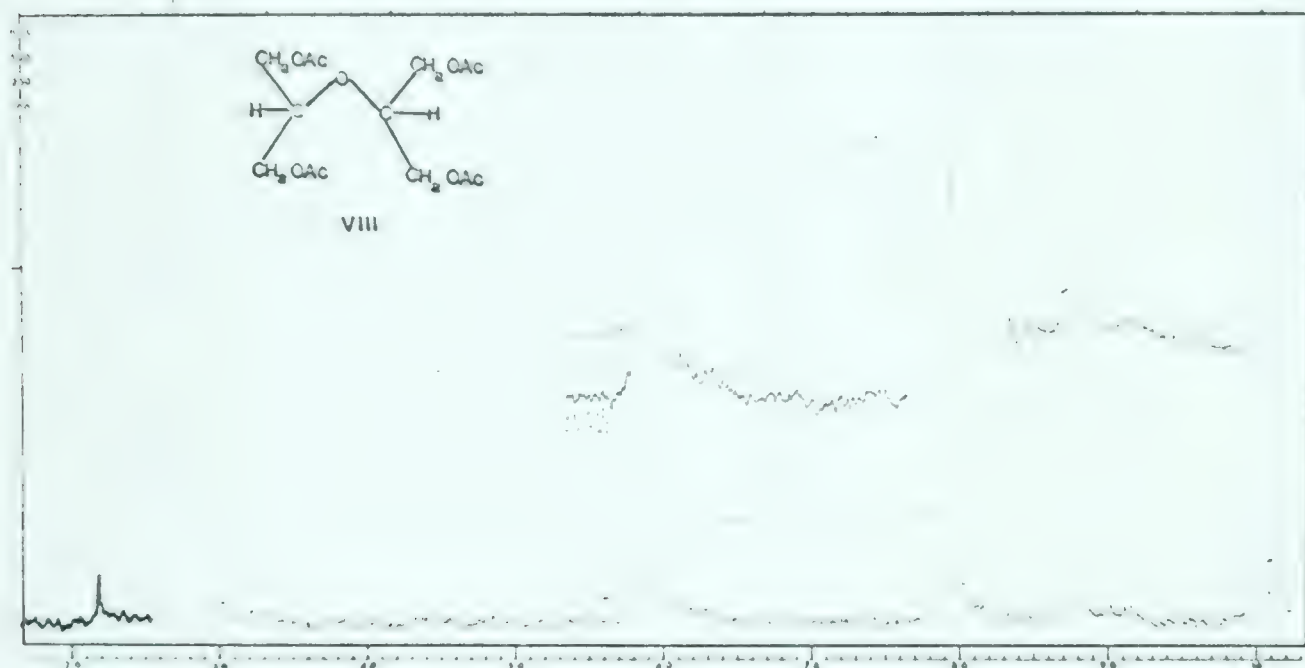


Fig. 8 Diglycerol Tetraacetate

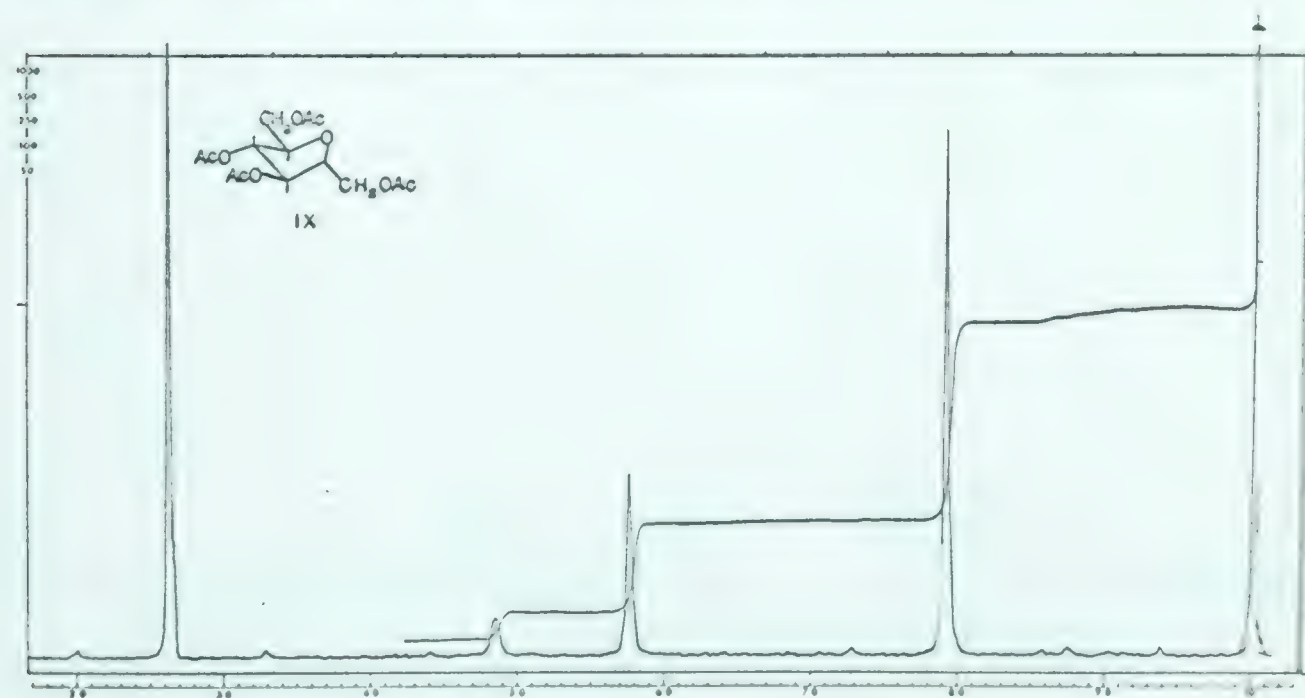
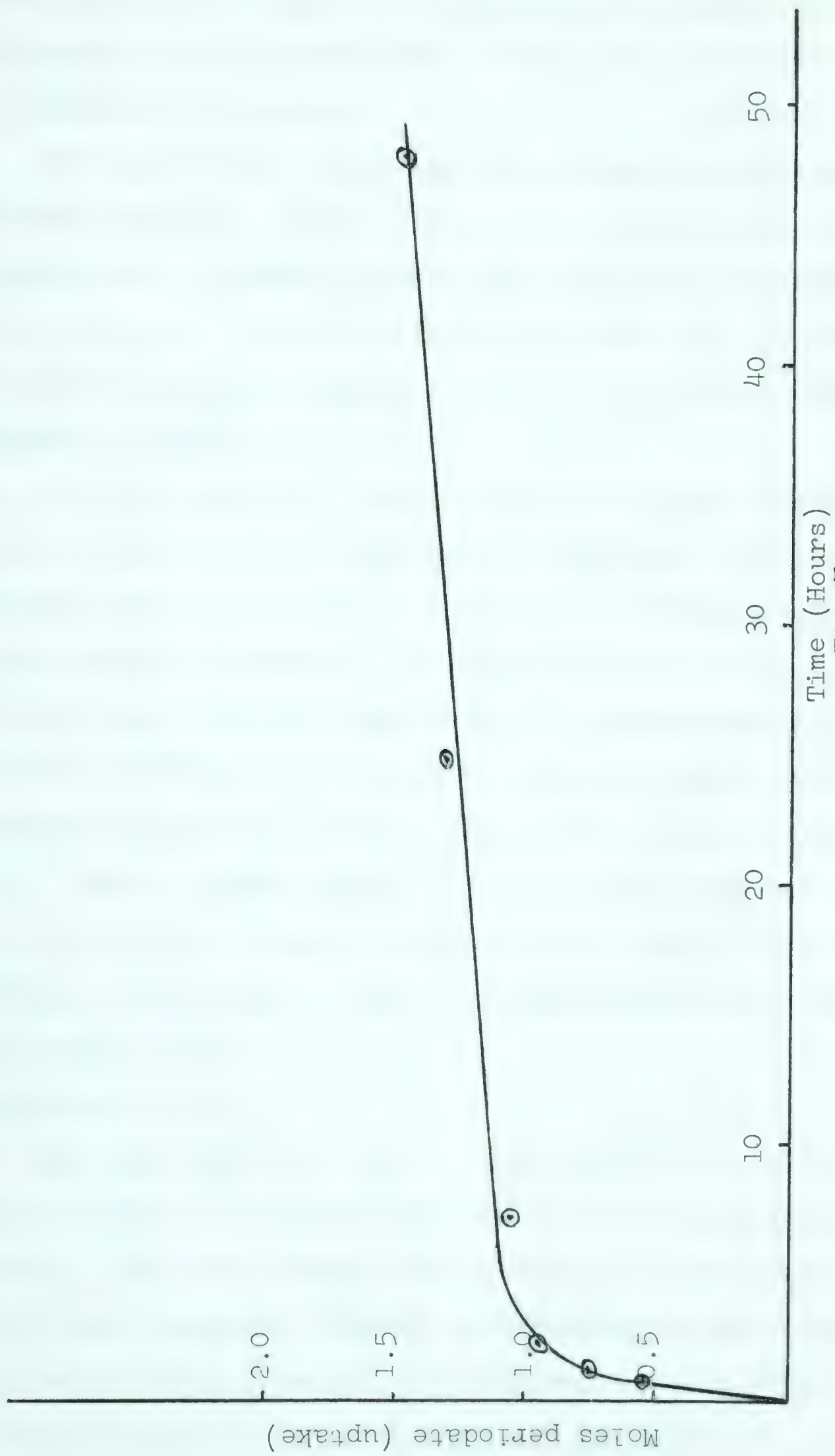


Fig. 9 2,5-Anhydro-D-mannitol Tetraacetate





Periodate Oxidation of the Dimethyl Acetal of  
2,5-Anhydro-D-mannose  
Fig. 7



the p-anisidine spray reagent. Hydrolysis by heating 10 mg of the material in 0.5N sulphuric acid (5 ml) on a steam bath was found to destroy the compound.

One half of the remaining 152 mg was reserved for analysis by periodate oxidation and the other half on acetylation with acetic anhydride in pyridine showed that the ratio of methoxy to acetoxy in the n.m.r. spectrum (Fig. 6) was now 2:3. This triacetate (VI) had a specific rotation of  $47.7^{\circ}$  ( $c$ , 1.39 in chloroform).

## 2. Periodate Oxidation of V

A 33 mg sample of V was dissolved in water (50 ml) and, after the addition of 10 ml 0.1M sodium periodate, the solution was diluted with water to 100 ml (volumetric). A blank of distilled water was similarly prepared. At intervals 5 ml aliquots of each solution were pinetted into 25 ml of phosphate buffer (pH 7) and after the addition of 10 ml of 10% aqueous potassium iodide, the liberated iodine was titrated with 0.01N sodium thiosulphate solution. Within 5 hours (Fig. 7) one mole of periodate was consumed; but slow over-oxidation during the next 50 hours caused an increase in this value. Tests for formaldehyde (25) and formic acid (26) were negative.

## 3. Methylation of V

The remainder of V, 43 mg, was treated for 18 hours with 4 ml methyl iodide in dimethylformamide (2 ml) containing silver oxide (5 g). The fully methylated material, 37 mg, obtained thereby (27) was shown by infrared spectroscopy to be different from both methyl tetra-O-methyl-  $\alpha$ -D-glucopyranoside (28) and methyl tetra-O-methyl-  $\alpha$ -D-mannopyranoside (29).



## III. 2,5-Anhydro-D-mannitol (VII)

## 1. From products of brominolysis

A 4.10 g sample of the brominolysis product containing IV $\alpha$  and  $\beta$  was reduced and deacetylated with sodium borohydride (10 g) in 50% aqueous methanol (100 ml) in the previously described manner [section C-III3]. Paper chromatographic examination of the reduced material, 1.01 g, showed the presence of at least six components with the main zone at  $R_f$  0.66. The material was chromatographed on a cellulose column using 5% petroleum ether in *n*-butanol and the first 980 ml of eluate yielded 111 mg of a mixture. The next 680 ml contained 615 mg of the desired component. Its infrared spectrum was identical to that of 2,5-anhydro-D-mannitol (VII) described below in section D-III2.

A 200 mg sample of the syrupy material was treated with 50 ml of 0.1 M sodium periodate solution for 3 hours. The solution was then evaporated in vacuo to dryness, and the residue extracted several times with hot ethanol. The combined ethanolic extracts were then treated with sodium borohydride (about 1 gram) and after 0.5 hour when a Fehling's test was negative, the reduced material was recovered (see section C-III3) and purified by acetylation with acetic anhydride in pyridine. The product, 97 mg, had a specific rotation of  $0.18^\circ$  ( $c$ , 3.3 in chloroform). Reported value (30) for this substance is  $0^\circ$ . The n.m.r. spectrum, Fig. 8, showed a single signal for four acetoxy groups at 7.9  $\tau$  and 10 protons in the vicinity of 5.9  $\tau$ . The spectrum therefore accords with the structure of the diglycerol tetraacetate, VIII, wherein the 8 methylene and 2 methine protons occur in the vicinity of 5.9  $\tau$ .



Acetylation of VII with acetic anhydride in pyridine gave a syrupy tetraacetate, IX,  $[\alpha]_D^{25} 26.4^\circ$  ( $c$ , 3.99 in chloroform).

## 2. From D-Glucosamine

2,5-Anhydro-D-mannose (chitose) was prepared by nitrous acid deamination of D-glucosamine using the method of Bera and coworkers (30). However, instead of neutralization with tertiary amine (which was found unworkable by the author because of the impossibility of freeing the desired product from amine salts), the acidic reaction mixture was titrated with saturated sodium bicarbonate solution to the end point of bromothymol blue. The solution was then concentrated to about 200 ml and 12.5 g of sodium borohydride was added. After 30 minutes, the reduced material was recovered in the usual manner (section C-III3) and its behavior on paper chromatograms was similar to that of the mixture described in section D-III1. Cellulose chromatography of 1.84 g of the product as above yielded 0.980 g of 2,5-anhydro-D-mannitol (VII). Acetylation gave a syrup, IX,  $[\alpha]_D^{25} 27.3^\circ$  ( $c$ , 4.18 in chloroform) whose n.m.r. spectrum (Fig. 9) showed three sharp signals at 5.17 (3- and 4-hydrogens), 4.25 and 8.12 (acetyl-hydrogens) tau of relative intensities 2:6:12 as expected for tetra-O-acetyl-2,5-anhydro-D-mannitol should the signals for the six hydrogens at the 1-, 2-, 5- and 6- positions show no chemical shift and occur at 4.25 tau.

## E. Brominolysis of Methyl 2-Deoxy-2-iodo- $\alpha$ -

### D-mannopyranoside Triacetate

#### I. Sodium Borohydride Reduction

The 2-iodo mannoside used in these preparative reactions was obtained by "direct" iodomethoxylation of D-glucal triacetate



in the presence of collidine (see Part I: section B-II). The majority of the  $\beta$ -D-gluco isomer was removed by fractional crystallization of the deacetylated material as described in section C-V of Part I. Nevertheless, the starting material usually contained about 8% of the gluco-isomer. Brominolysis of 9.1 g (21 mM) of this mixture using threefold quantities of the reagents prescribed in section C-II yielded 6.52 g of syrupy product.

Treatment of the material with methanolic hydrogen chloride or methanolic ammonia for seven hours led to a maze of deacetylated compounds. Examination of the product by reverse phase chromatography showed at least ten components, one of which reacted intensely with the alkaline silver nitrate spray; however, upon hydrogenolysis of the brominolysis product (147 mg in 20 ml of methanol containing 30 mg of Adams' catalyst) this intense reactant disappeared. Attempts at fractionation on a column of silicic acid impregnated with dimethyl sulphoxide as in section D-I were unsuccessful.

The material, 5.00 g, was therefore reduced with sodium borohydride as described in section C-III3. The product, 2.0 g, showed five main components, one of which,  $R_f$  0.71, was evidently the starting material. The others had  $R_f$  values of 0.18, 0.30, 0.53 and 0.65 and these were separated on a cellulose column using n-butanol-Skellysolve-B (4:1) mixture for development. The 175 - 300 ml region yielded 1.03 g of the fastest moving component ( $R_f$  0.65), XI, and the 594-723 ml region gave 0.23 g of X ( $R_f$  0.30). The other two components,  $R_f$  0.18 and 0.53, were not well resolved on the chromatogram.



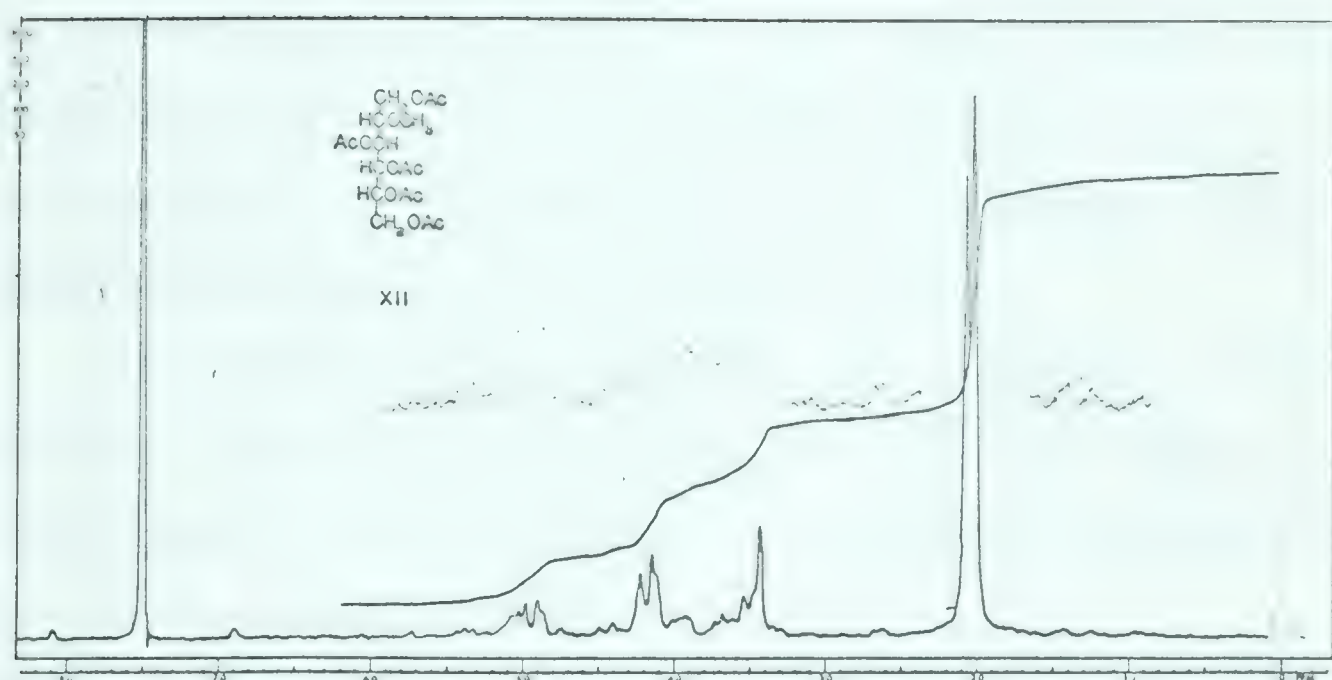


Fig. 10 2-O-Methyl-D-glucitol Pentaacetate



## 1. Characterization of a 2-O-Methyl Hexitol

The compound X was acetylated and the product, XII was found by n.m.r., Fig. 10, to contain five acetoxy groups per methoxy group. Oxidation of 15.4 mg of X with sodium periodate (cf section D-II2) consumed 3.28 moles of periodate and liberated 2.2 moles of formic acid and 1.1 mole of formaldehyde per mole, Fig. 11. A portion of the oxidized material was analyzed by paper chromatography and a canary yellow spot was revealed by the aniline phthalate reagent (31) with the  $R_f$  0.78 of 2-O-methyl glyceraldehyde (32). It was therefore concluded that X was a 2-O-methylhexitol. The parent compound 2-O-methyl-D-glucose was characterized as described in section E-II.

On the assumption that no other component of the sodium-borohydride - reduced material was producing formaldehyde, the 2-O-methyl hexitol was estimated, by periodate oxidation, to constitute 20.4% of the product.

## 2. Methyl 2-Bromo-2-deoxy- $\alpha$ -D-altropyranoside, and 2-Deoxy-D-allose

The major component (XI,  $R_f$  0.65) obtained from the cellulose column chromatogram was acetylated. The n.m.r. spectrum of the product (XIII) in chloroform, Fig. 12, showed the presence of three chemically shifted O-acetyl groups and one O-methyl group. Qualitative tests revealed the presence of bromine. Hydrogenolysis of XI, 320 mg, over 5% palladium on charcoal in 50 ml of 50% aqueous methanol containing 0.2 ml of triethylamine, afforded 110 mg of a substance which on paper chromatography gave the color reaction with the p-anisidine hydrochloride spray reagent found characteristic for methyl 2-deoxyhexosides. The latter, XIV, was neither methyl 2-deoxy- $\alpha$ - or  $\beta$  -D-glucopyranoside as shown



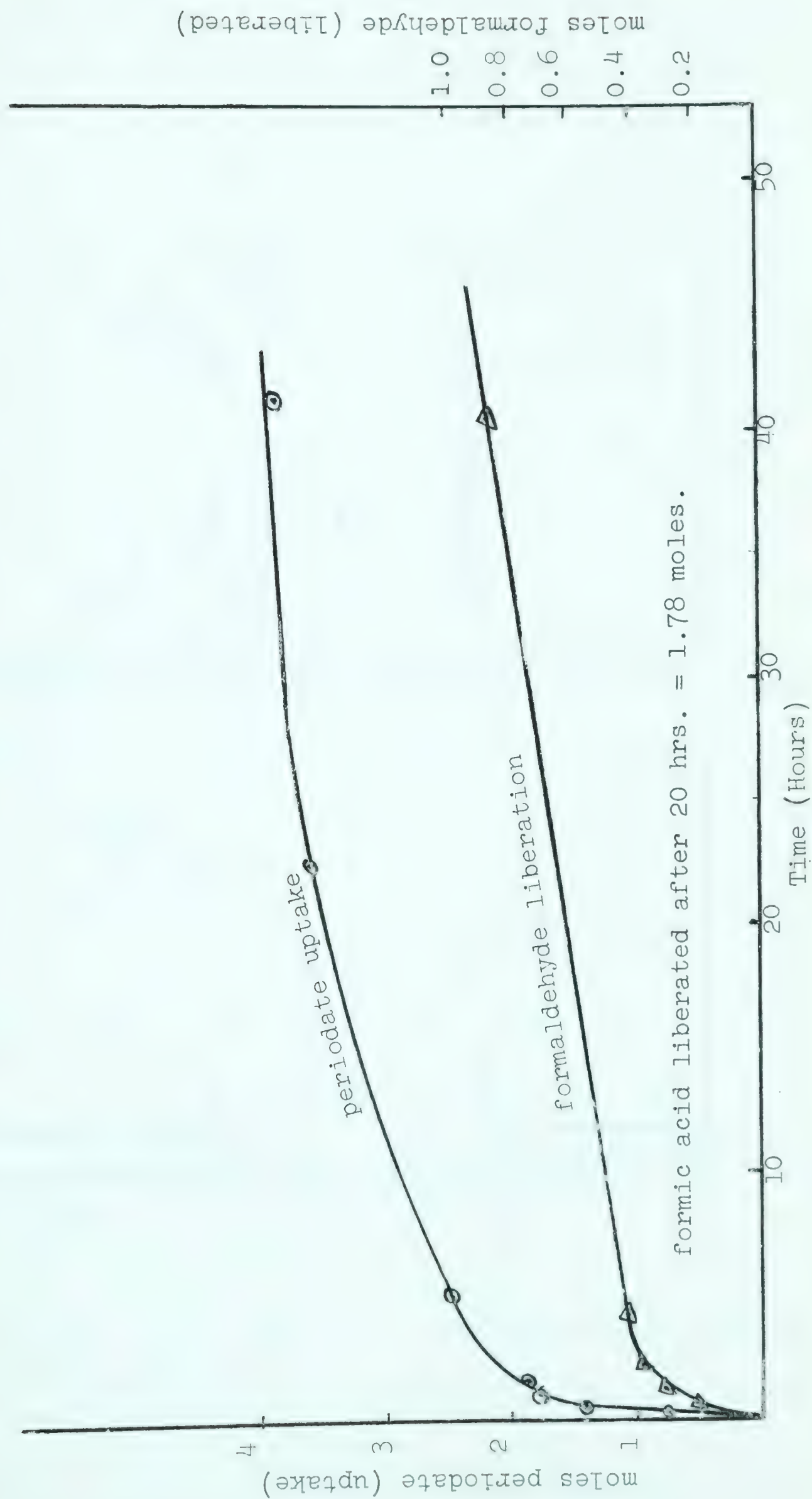


Fig 11

Periodate Oxidation of 2-O-Methyl-D-Glucitol



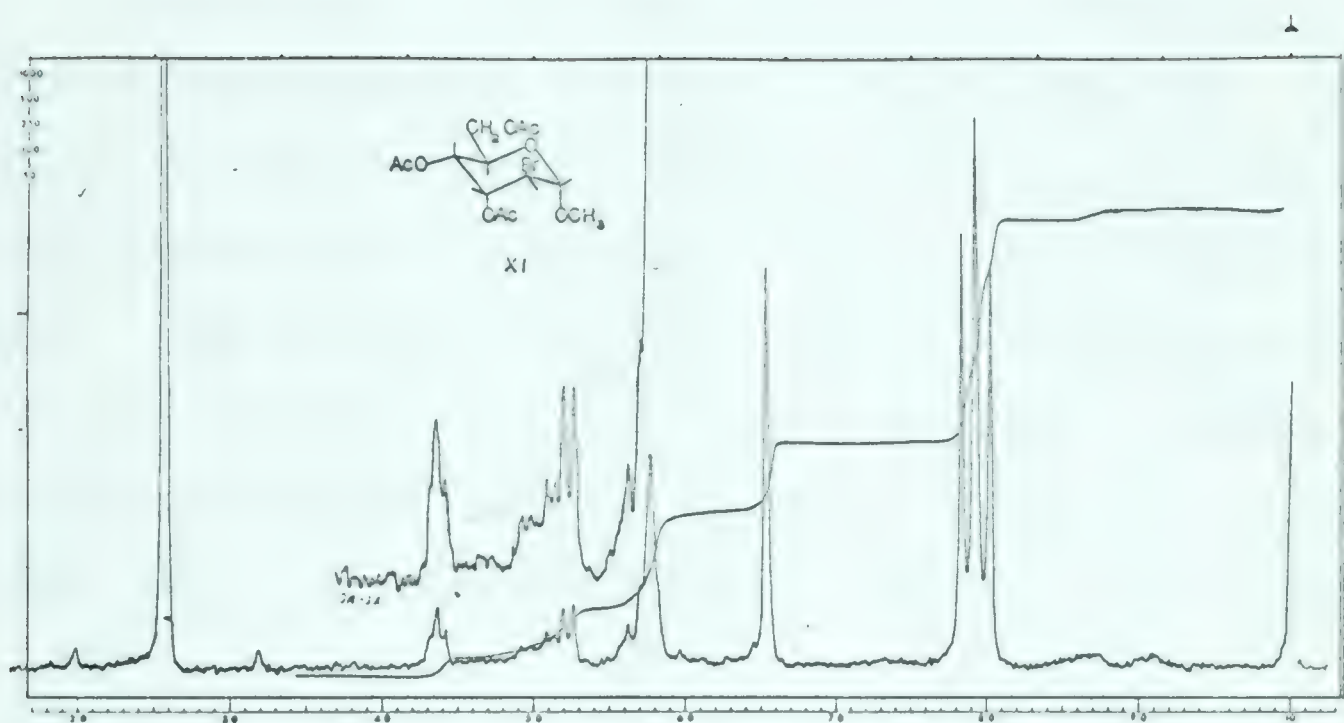


Fig. 12 Methyl 2-Bromo-2-deoxy-α-D-altropyranoside Triacetate

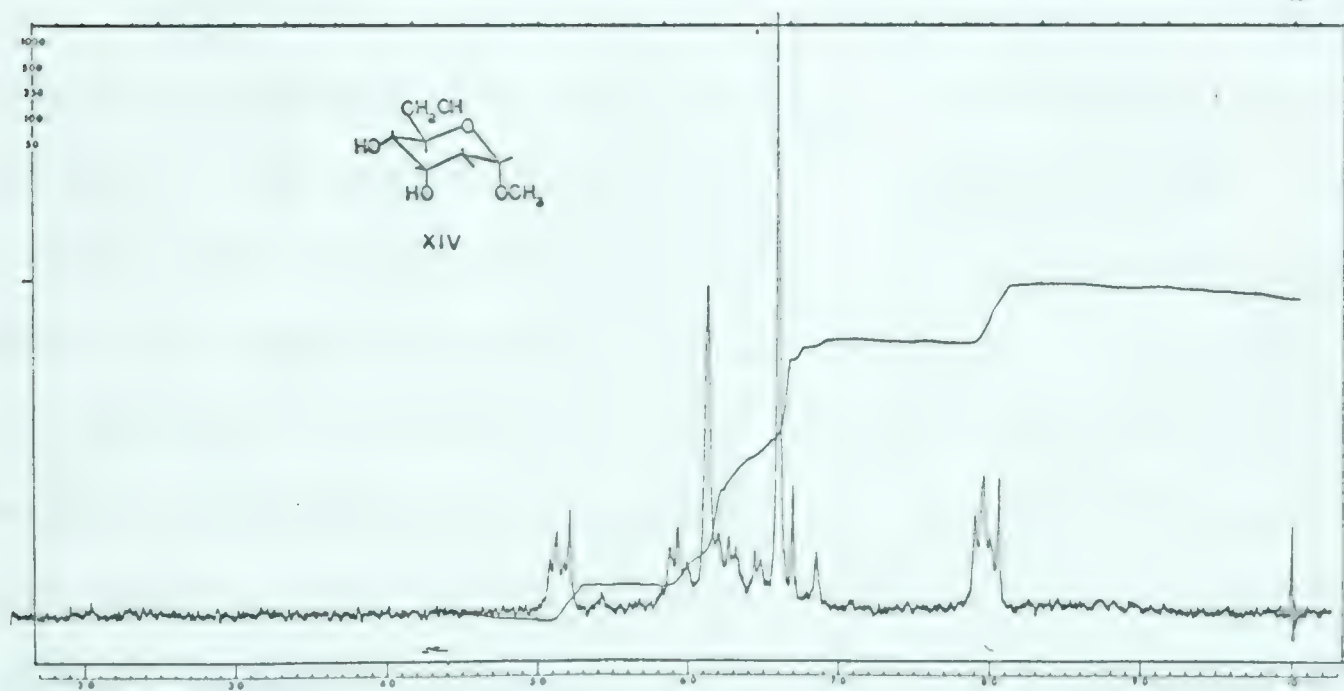


Fig. 13 Methyl 2-Deoxy-α-D-allopyranoside



by comparison of their n.m.r. spectra measured in deuterium oxide (Fig. 13). The specific rotation of methyl 2-deoxy- $\alpha$ -D-allopyranoside,  $144^{\circ}$ , compared favorably with that of the 2-deoxy hexoside,  $146^{\circ}$  ( $c$ , 1.2 in methanol).

Hydrolysis of XIV with cold normal sulphuric acid was complete after four hours (constant optical rotation). Neutralization of the acid with basic Amberlite IRA-400 followed by filtration and evaporation *in vacuo* gave a syrup which crystallized from ethanol. The melting point after four recrystallizations from ethanol was  $135-136^{\circ}$ ,  $[\alpha]_D 55.2^{\circ}$  ( $c$ , 1 in water), and was not depressed when admixed with an authentic sample (33) of 2-deoxy-D-allose, XV. The reported constants are m.p.  $133-5^{\circ}$  and  $[\alpha]_D 57.9 \pm 2^{\circ}$ .

### 3. Methyl 3,6-Anhydro- $\alpha$ -D-glucopyranoside

Treatment of XI, 150 mg, with 5 ml of 0.75 N sodium methoxide in methanol for nineteen hours followed by neutralization of the base with sulphononic acid resin in the acid form, filtration, evaporation and fractionation of the resulting mixture (99 mg) on Whatman 3 MM paper afforded 9 mg of a compound,  $R_f$ , 0.84, which had an identical infrared spectrum to that for methyl 3,6-anhydro- $\alpha$ -D-glucopyranoside (XVI) prepared from methyl 6-O-tosyl- $\alpha$ -D-glucopyranoside (34) by the method of Haworth and coworkers (35). The trans-D-altro configuration for the 2,3-bromohydrin was therefore established.

## II. Zinc Dust Reduction

1. Methyl 3-Acetoxy-2-bromo-2-deoxy- $\alpha$ -D-arabino-hexopyranoside Triacetate, and Methyl 2-Deoxy- $\alpha$ -D-erythro-hexopyranoside-3-ulose Diacetate

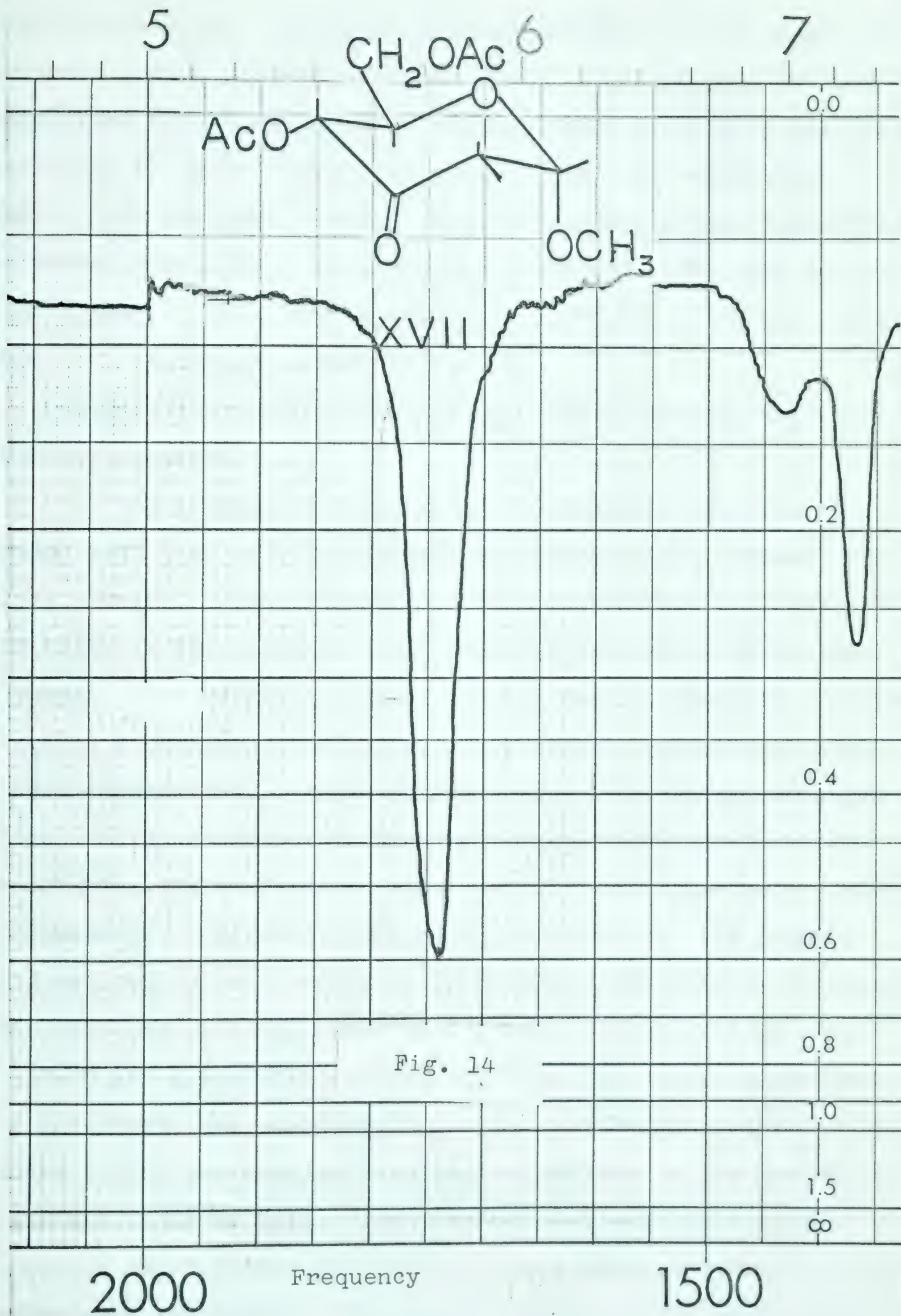


A solution containing 4.4 g of the syrupy product of brominolysis in 20 ml of glacial acetic acid was prepared. A 5 ml aliquot of this solution was added to a well-stirred mixture of 6 ml water, 3 ml glacial acetic acid and 0.6 g zinc dust at 0°. After one hour, 1.2 g zinc dust, 5 ml water and a further 5 ml portion of the above solution were added to the reaction mixture. Addition of similar quantities of these substances was made twice during the succeeding two hours, after which the mixture was allowed to stand with stirring at room temperature for an additional fifteen hours. Excess zinc dust and precipitated salts were removed by filtration and the filtrate was exhaustively extracted with chloroform. The chloroform phase after being washed to neutrality with water was dried and evaporated in vacuo to yield 2.71 g of a syrupy, halogen-free product which, according to its infrared spectrum, reproduced in Fig. 14, did not contain an olefinic bond as would be expected with XVIII. The product was readily deacetylated on standing for two hours in a mixture of methanol, water and triethylamine (50:45:5). Paper chromatography of the deacetylated material showed a very intense spot ( $R_f$  0.57) with either p-anisidine or alkaline silver nitrate spray reagent. Sodium borohydride reduction of the deacetylated material, and isolation as described (in section C-III3) led to a product which on paper chromatograms had color reactions characteristic for a methyl 2-deoxyhexoside.

2. Semicarbazone of XVII

The material from the zinc dust reduction, 1.30 g, was dissolved in 5 ml of ethanol and water was added until a turbid







solution resulted. Semicarbazide hydrochloride, 0.75, and 1.19 g anhydrous sodium acetate were then added. On standing at room temperature for thirty minutes, crystals were deposited, and after cooling at 0° for a further two hours, 0.40 g of crystalline material was isolated. After four recrystallizations from ethanol, the material XIX had a melting point of 195-6°,  $[\alpha]_D^{25}$  146° (c, 0.75 in pyridine). Calc. for  $C_{12}H_{19}N_3O_7$ : C, 45.43; H, 5.99; N, 13.25%. Found: C, 45.67; H, 5.88; N, 13.08%.

### 3. 2-O-Methyl-D-glucose Tetraacetate, and 2-O-Methyl-D-glucose Diethyldithioacetal

The product, 0.5 g, of the brominolysis reaction was treated with 5 ml of 0.05 N sodium methoxide in dry methanol for thirty minutes. The solution was then neutralized with sulphonhic acid resin in the acid form, filtered and evaporated to dryness in vacuo. The resulting syrup, 110 mg, was treated with a mixture of 0.5 ml ethanethiol and 0.5 ml concentrated hydrochloric acid at room temperature. After fifteen hours, 5 ml water was added to the cooled solution and the excess ethanethiol was removed. The solution was neutralized with basic ion exchange resin (Amberlite IRA-400). After filtration and evaporation, the product was dissolved in ethyl ether to deposit 13.2 mg of material which, after four recrystallizations from ethanol, had a melting point of 157-8° and a specific rotation of -22.4° (c, 0.52 in pyridine).

D-glucose was converted to its diethyldithioacetal (36) and the latter was methylated at the 2-position by the method of Lieser and Leckzyck (37). This material gave no melting point depression on admixture with than obtained above, and their infrared spectra were identical. The n.m.r. spectrum of XX is shown in Fig. 15.



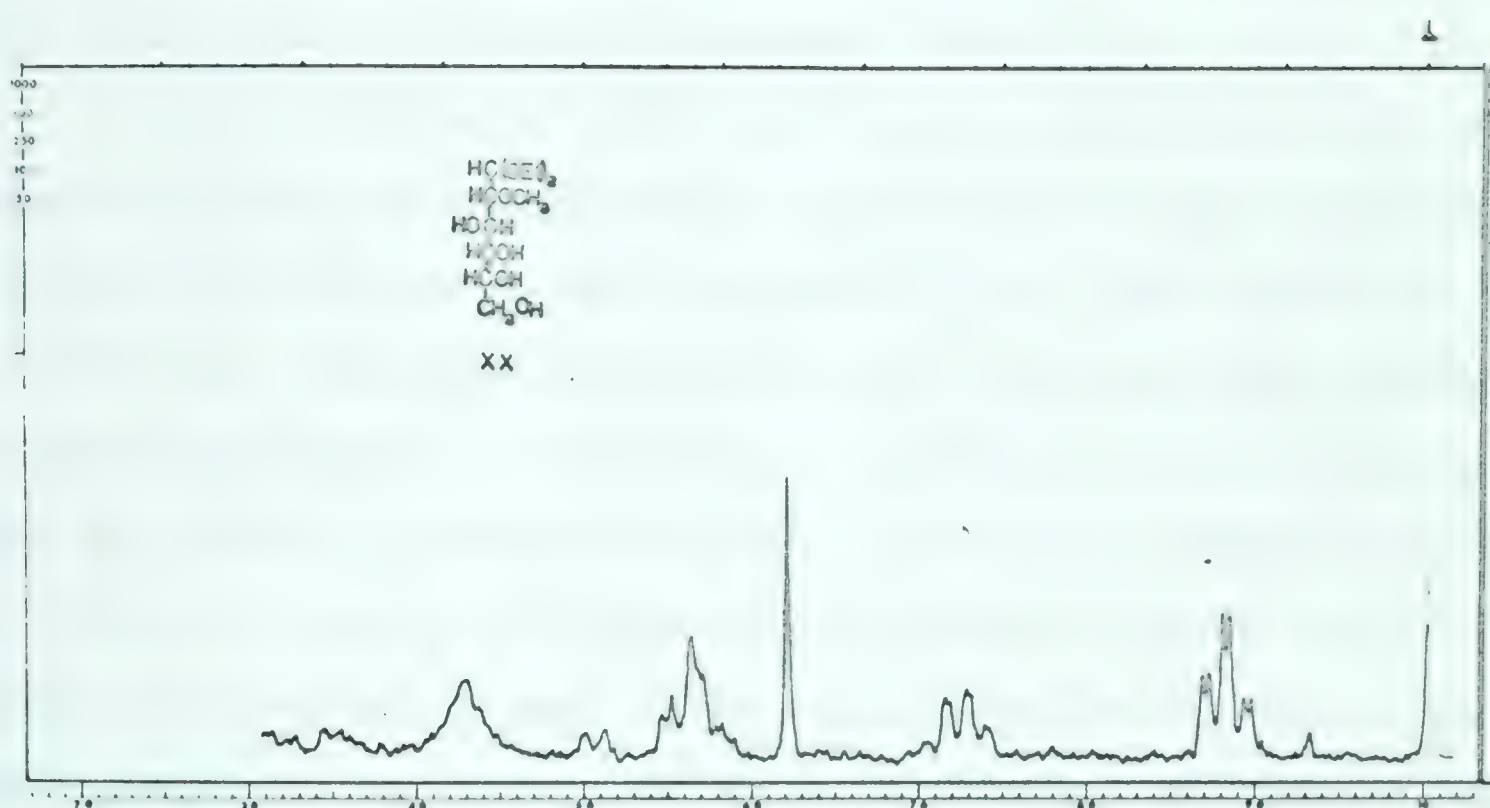


Fig. 15 2-O-methyl-D-glucose Diethyl Dithioacetal



## DISCUSSION OF RESULTS

The conditions developed (2, 4) for alkoxyl determinations using bromine was a convenient launching point for the investigations. Although the rate of reaction of simple alkyl iodides with bromine in these conditions is extremely rapid, (as was shown by control experiments on methyl iodide), deiodination of 2-iodo-glycosides was only 11.6 per cent complete in one week. The process could be accelerated by heating, but the rate (37% in 24 hours) was still uselessly slow.

If the kinetic studies of Keefer and Andrews (12) on isopropyl iodide also applied in the reactions under investigation, the first step would be the formation of the iodoso dihalide (Scheme 2). The rate determining step, in which this complex is oxidized by halogen (or in Scheme 4 by  $\text{ICl}$ ), was evidently proceeding too slowly in these reactions, and it was surmised that the addition of a potent electrophile, for example silver ion, might promote the oxidation more efficiently than the halogen. An additional salutary effect would be the removal of bromide ions as competing nucleophiles by formation of insoluble silver bromide; nucleophilic attack by acetate ions would thereby be facilitated. This procedure proved in fact, to enhance the rate of reaction greatly and comprises evidence that the rate controlling stage in the brominolysis of an iodide involves the formation of a bromo-iodonium cation (Scheme 4). The silver precipitates were found to be free from iodide ions; that the iodine was in fact oxidized was confirmed since the solution could be titrated for iodate in the normal manner.

The reaction conditions found most advantageous for



preparative purposes are described in section C-II of the experimental. However, it was desirable to achieve better insight into the essential mechanism of the brominolysis reaction and therefore a number of experiments were conducted on simple iodides. The first of these was the primary carbohydrate iodide methyl 6-deoxy-6-iodo- $\alpha$ -D-glucopyranoside triacetate (I).

The probable constituents of the brominolysis were the 6-bromo and 6-acetoxy derivatives (II and III, respectively) as well as the starting material, Fig. 2. Since the methoxy signals for these three compounds were chemically shifted at 100 Mc.p.s., Fig. 3, their presence in the reaction product could be conveniently followed.

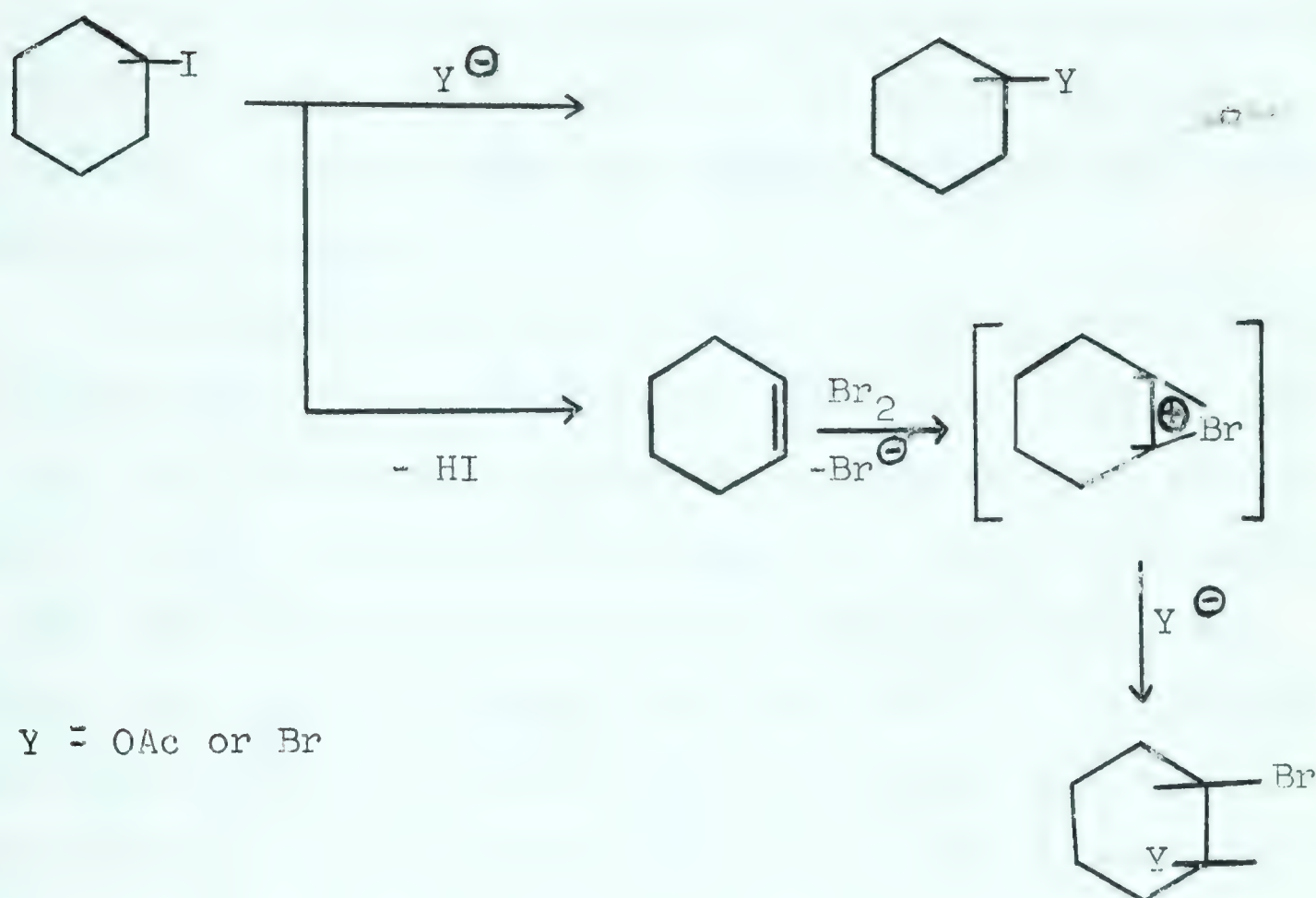
In one experiment, the compound (I) was treated with a 5 mole excess of bromine (0.13 M) in N-potassium acetate in acetic acid. After seven hours, reaction was complete and the product was a 1.1:1 mixture of methyl 6-bromo-6-deoxy- $\alpha$ -D-glucopyranoside triacetate (II) and a methyl  $\alpha$ -D-glucopyranoside tetraacetate (III). When the reaction mixture was diluted ten fold with the potassium acetate in acetic acid solution to reduce the initial bromine concentration to 0.013 M, the reaction after seven hours was only about 44% complete. The relative amounts of the 6-bromo (II) and 6-acetoxy (III) reaction products was now 0.4:1, respectively. The brominolysis reaction under these dilute conditions was complete after 43 hours and the reaction product was a 0.6:1 mixture of the 6-bromo (II) and 6-acetoxy (III) products, respectively. These experiments clearly show that the 6-bromide is to some extent formed by way of an attack by external bromine and/or bromide on the reactive intermediate. The reaction was then conducted



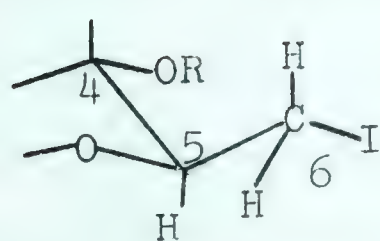
under the same conditions of dilution but in the presence of two moles of dissolved silver acetate per mole of bromine in order to exclude any possibility of the presence of bromide ion. The reaction product was analytically pure methyl  $\alpha$ -D-gluconopyranoside tetraacetate. In view of the fact that the brominolysis reaction is second order in bromine (12), the reduction in the extent of replacement by bromine on a ten fold dilution of the reaction mixture was not as great as would be expected unless the bromide is formed extensively by attack on the reactive intermediate by a bromide ion from the immediate environment. It is evident, therefore, that the retention mechanism is operative to an important extent in these reactions. Evidently, the iodine may be replaced by acetoxy with retention in the reactions conducted in the presence of silver acetate. The brominolysis of the 6-iodide under the same conditions as were used for the 2-iodide (section C-II) gave an 0.82:1 ratio of the 6-bromo and 6-acetoxy products, respectively.

Cyclohexyl iodide was an obvious choice as a model compound since the competition between elimination and replacement reactions on this cyclic structure would be instructive. Cyclohexyl bromide, cyclohexyl acetate, trans-cyclohexene dibromide and trans-2-bromo cyclohexyl acetate were all produced (Fig. 4), and it was evident from the proportions of these products (4.3, 6.7, 34.4 and 54.6% respectively) that elimination was a main course of reaction, Scheme 5. The intermediate olefin reacted, of course, in these conditions. In the reaction of the 6-iodo sugar described in the preceding paragraph, no evidence of elimination to form the 5,6-glucosene (38) XXI, (Scheme 6) was

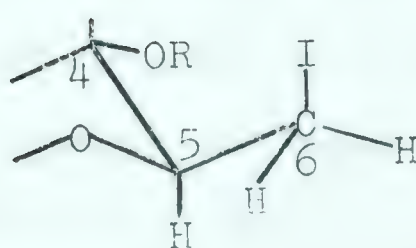




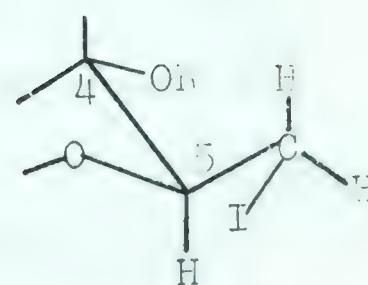
Scheme 5



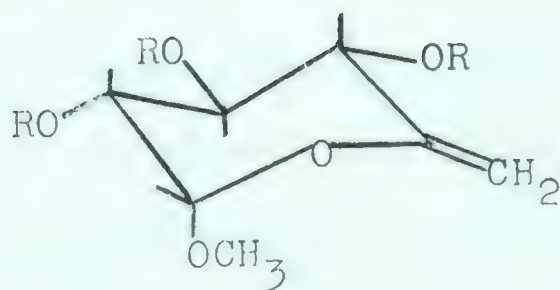
Ia



Ib



Ic



XXI

R = Ac

Scheme 6



observed. The rotomer I(b), from which elimination would most readily occur, is obviously favourably disposed for nucleophilic substitution at the primary carbon as the iodide undergoes brominolysis. In comparison, the rotomers I(a) and I(b) would be much less favourable.

The product from brominolysis of methyl 2-deoxy-2-iodo- $\beta$ -D-glucopyranoside triacetate was a less complex mixture than that from the corresponding mannoside. Reverse phase chromatography on paper indicated the presence of two main components, and these were isolated by preparative chromatography. Both compounds gave negative halogen tests and their n.m.r. spectra proved to be remarkably similar (Fig. 5). Each contained a methoxy group and four acetoxy groups, but their extreme lability to acids and bases rules out the possibility of methyl hexopyranoside tetraacetate skeleton. The presence in both, of low field doublets, was reminiscent of an anomeric proton deshielded strongly by an electron-withdrawing group (see Part I). This raised the possibility that the glycosidic methoxyl group had migrated to carbon-2 with the subsequent production of the alpha and beta anomeric glycosyl acetates. This conjecture seemed plausible because treatment with methanolic hydrogen chloride and subsequent reacetylation converted both compounds into a single substance, VI, whose n.m.r. spectrum, Fig. 6, now showed the presence of two methoxy and three acetoxy groups. Furthermore, the new glycoside (V) rapidly consumed one mole of sodium periodate (Fig. 7), and produced neither formaldehyde nor formic acid. However, its strong reaction with p-anisidine on paper chromatograms, was inconsistent with the structure of a simple methyl 2-O-methyl hexopyranoside. The possibility of a methyl 2-O-methyl



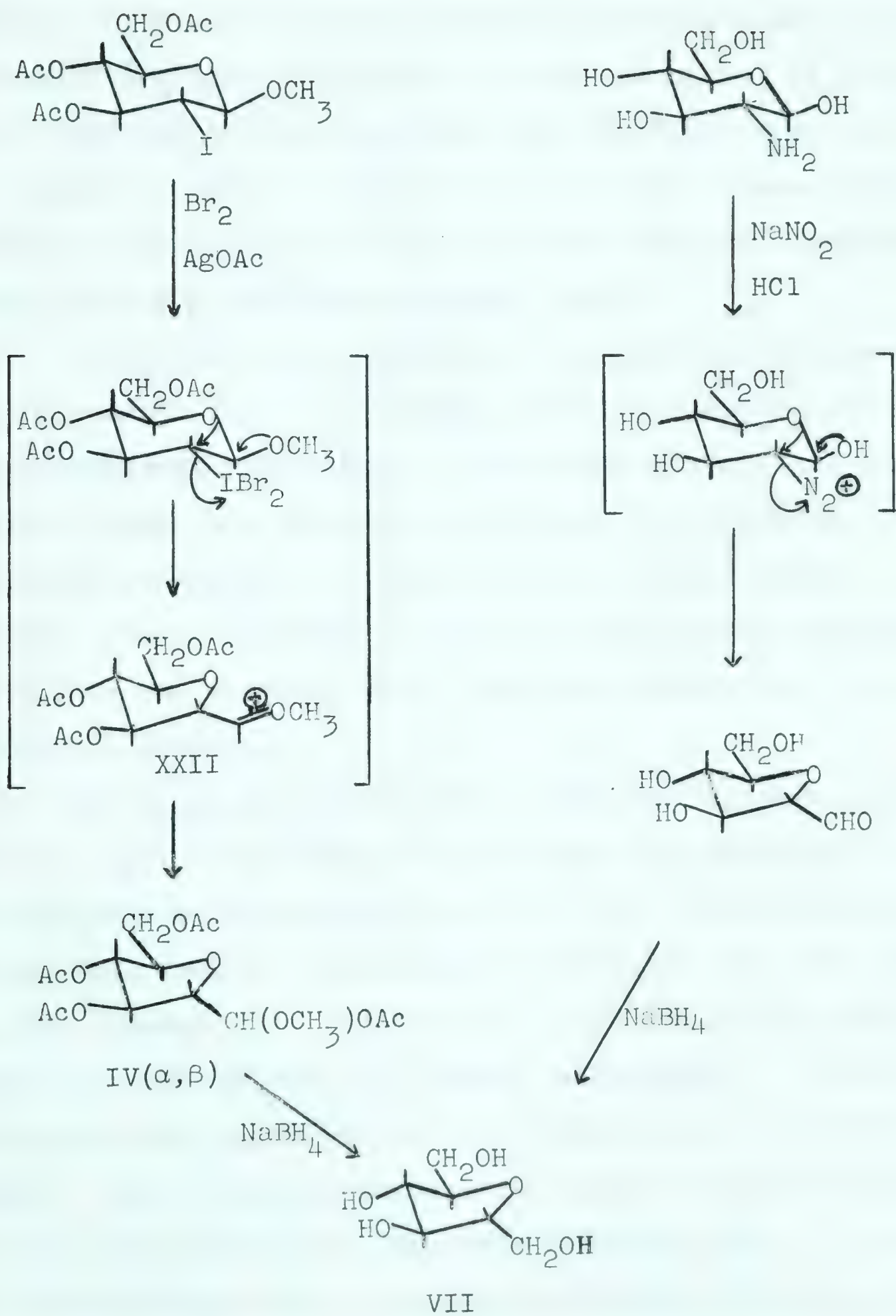
sugar was finally rejected when full methylation of V produced neither methyl tetra-O-methyl- $\alpha$ -D-glucopyranoside nor mannopyranoside, since it was inconceivable that the glycosidic methoxyl, if it had indeed migrated, could have been located on any other than carbon-2.

The possible trans-annular migration of the lactol ring oxygen was contemplated. It is well established (39, 40) that migration proceeds most favorably when the migrating and the leaving groups define a dihedral angle of  $180^\circ$ . In the methyl 2-iodo glucoside the lactol ring oxygen and the leaving iodine meet this unique requirement, Scheme 7, and trans-annular migration to yield the 2-5-anhydro-D-manno skeleton is therefore possible.

The existence of the oxocarbenium ion, XXII, as a discrete reaction intermediate is indicated by the fact that equimolar amounts of both enantiomers ( $IV^\alpha$  and  $IV^\beta$ ) were formed, Fig. 5. In accordance with the original basis for naming anomeric compounds derived from D-sugars (41), the more dextrorotary compound ( $IV^\alpha$ ), was assigned the alpha-configuration and the other ( $IV^\beta$ ) the beta-configuration.

The course of the brominolysis reaction is analogous to the nitrous acid deamination of glucosamine to form chitose, Scheme 7. A resemblance between the intermediates in both processes, namely the iodoso dihalide and the diazonium ion respectively, seems to be implied. In fact, sodium borohydride reduction of either the brominolysis product of the 2-iodoglucoside or the deamination product from glucosamine gave 2,5-anhydro-D-mannitol (VII). In both cases the reduction was accompanied by rather severe degradation, but the degradation products were not investi-





Scheme 7



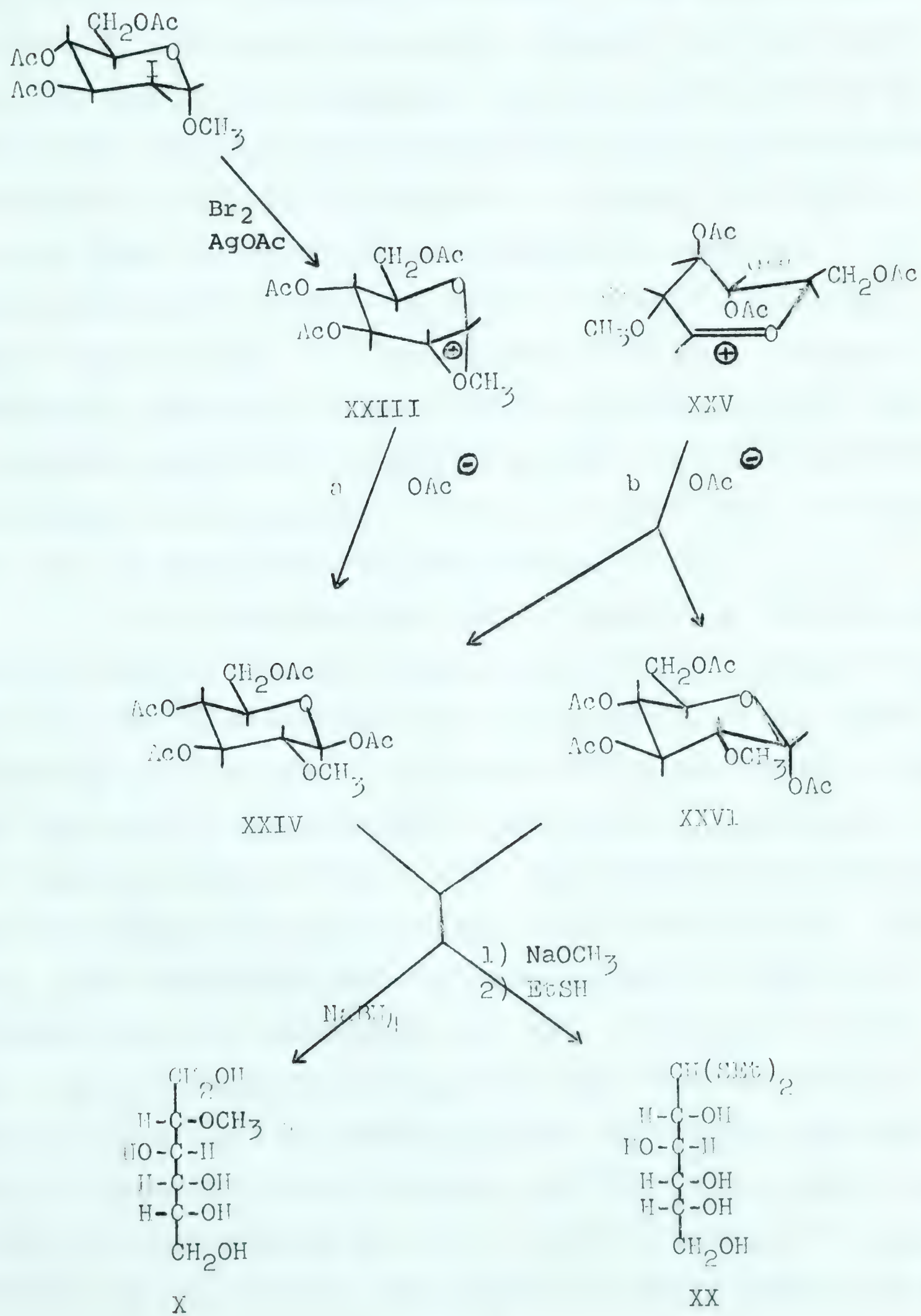
gated.

A portion of the 2,5-anhydro mannitol on periodate oxidation followed by sodium borohydride reduction and acetylation gave a tetraacetate with an optical rotation of zero. This is expected for the diglycerol tetraacetate, VIII, and its n.m.r. spectrum, Fig. 8, shows signals for four magnetically identical O-acetyl groups, and for 8 methylene and 2 methine protons of nearly equivalent chemical shifts.

Attention was now given to the much more complex reaction product from brominolysis of methyl 2-deoxy-2-iodo- $\alpha$ -D-mannopyranoside triacetate. Inspection of the crude product by n.m.r. showed the presence of at least five different methoxyl containing substances; the most intense methoxyl signal was at 6.48 tau. Chromatography on dimethyl sulphoxide impregnated paper showed the presence of at least ten components, one of which was starting material.

The trans-annular migration observed in the reaction of 2-iodo- $\beta$ -D-glucoside (Scheme 7) could have its counterpart here, since the glycosidic methoxyl group and the 2-iodine are in the coplanar antiparallel relationship conditional (39, 40) for migration (Scheme 8). With this in mind, the crude product was reduced and deacetylated with sodium borohydride. Column chromatography allowed the isolation of at least two of the five components. One of these substances appeared to be a 2-O-methyl-D-hexitol when examined by periodate oxidation (Fig. 11), and paper chromatography of the periodate-oxidized material gave a positive reaction for 2-O-methyl glyceraldehyde (32). In addition, the n.m.r. spectrum of the acetylated material (Fig. 10)





Scheme 8



showed the presence of five acetoxy groups and one methoxy group. It was decided on this basis to examine the product of the brominolysis reaction for 2-O-methyl-D-glucose. The material was deacetylated with sodium methoxide in methanol and the resulting syrup was treated with ethanethiol and hydrochloric acid in the anticipation that the well-characterized and high-melting diethyl dithioacetal derivative of 2-O-methyl-D-glucose, XX, could be isolated from the product of the mercaptolysis reaction. In fact, a crystalline product was readily isolated which melted some 20 degrees lower than the reported value (42). However, it possessed an identical infrared spectrum and melting point with an authentic sample of 2-O-methyl-D-glucose diethyl dithioacetal, XX, prepared from D-glucose. The n.m.r. spectrum of the material (Fig. 15) is consistent with the structure of XX.

It is therefore clear that a course of the brominolysis reaction involved cleavage of the axial C<sub>2</sub>-I bond, likely by way of a [C<sub>2</sub>-I-Br]<sup>⊕</sup> intermediate, with participation of the axial C<sub>1</sub>-methoxy group to lead to a 1,2-methoxonium ion (XXIII), Scheme 8. This ion would of course accept a nucleophile preferentially at the 1-position, Scheme 8(a). Thus, one product of the reaction may be 2-O-methyl-β-D-glucofuranose tetraacetate (XXIV). However, it is conceivable that the methoxonium ion is much less favorable than the oxocarbenium ion, XXV. (Scheme 8). Indeed, in Part I of this Thesis it was suggested that when the carbon-2 substituent is strongly electronegative, oxocarbenium ions such as XXV may predominate in the reaction, and its presence should lead to the formation (Scheme 8b) of α- (XXVI) as well as β- anomers (XXIV). It was, however, not possible to obtain information on

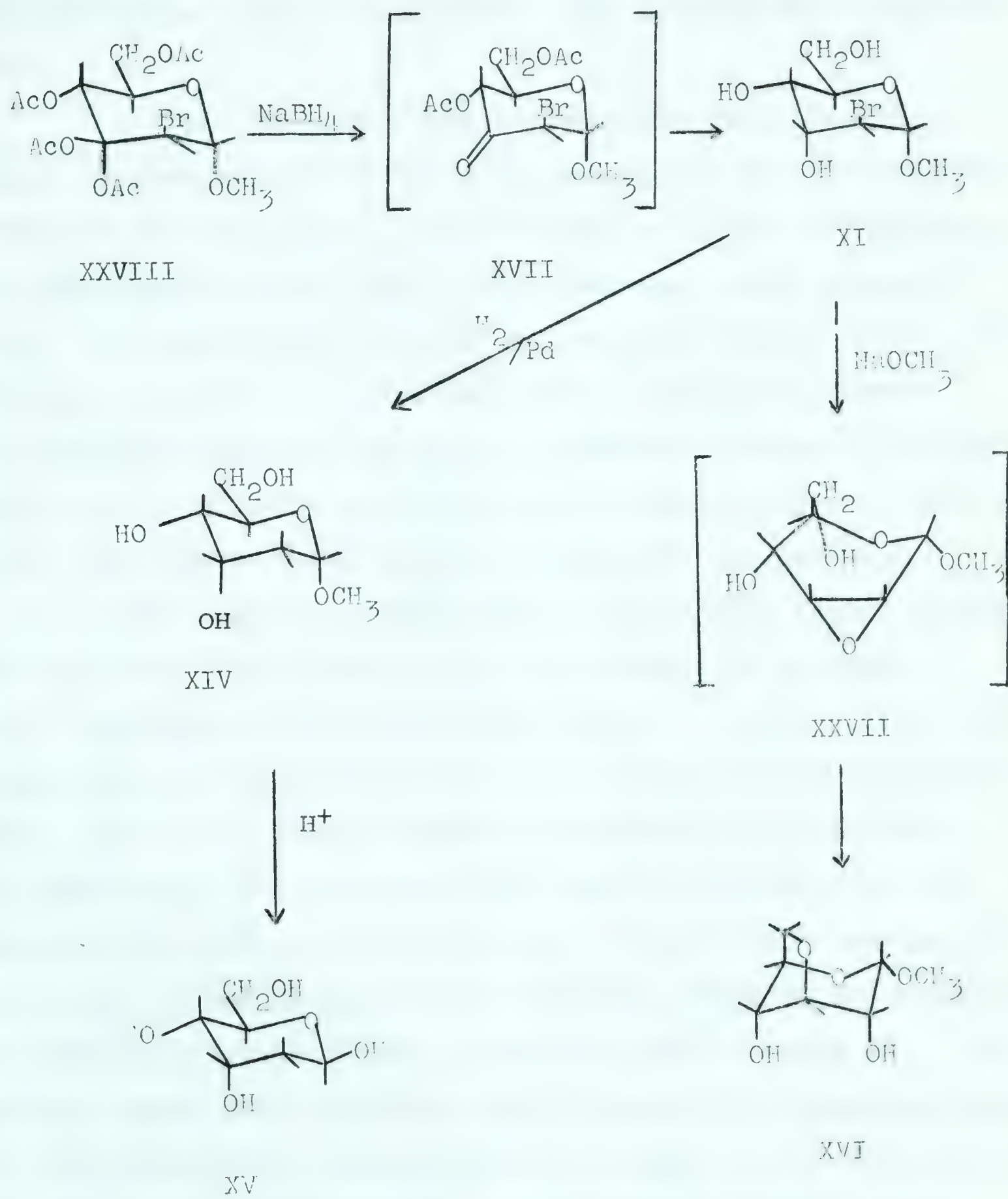


this matter. As far as can be ascertained, this is the first example of a methoxy group migration in carbohydrate chemistry, although Winstein and Ingraham (43) observed a methoxy migration in the silver ion assisted solvolysis of 2-methyl-2-methoxy-3-bromobutane. In both cases the migration occurred because the intermediate ethylene oxonium ion was preferentially attacked at the centre which was originally bonded to the methoxyl group.

The extent of migration was at least 11.5% - the actual yield of this material from the mixture placed on cellulose chromatogram. However, on the assumption that 2-O-methyl glucitol was the only component in the borohydride-reduced-material capable of producing formaldehyde, the migration was estimated, by periodate oxidation, to have proceeded to the extent of 20.4%.

The major component from the chromatogram, XI, failed to crystallize. The substance contained bromine, appeared pure on chromatograms, and the n.m.r. spectrum (Fig. 12) of the acetylated material (XIII) showed three acetyl groups per one methoxyl group. Hydrogenolysis of the bromine and deacetylation provided a methyl 2-deoxy-glycoside, Scheme 9, different from either methyl 2-deoxy- $\alpha$  - or  $\beta$ -D-glucopyranoside, but possessing the specific rotation reported for methyl 2-deoxy- $\alpha$ -D-allopyranoside (XIV), (44). Acid hydrolysis (Scheme 9) gave a 2-deoxy sugar found identical by direct comparison (33) with 2-deoxy-D-allose (XV), (44). It was therefore evident that the major compound from the chromatogram, XI, was a methyl 2-bromo-2-deoxy-D-hexopyranoside possessing either the altro- or allo-configuration. The D-altro-configuration was established by treatment of XI with sodium methoxide, Scheme 9, to form methyl 3,6-anhydro- $\alpha$ -D-glucoside.





Scheme 9



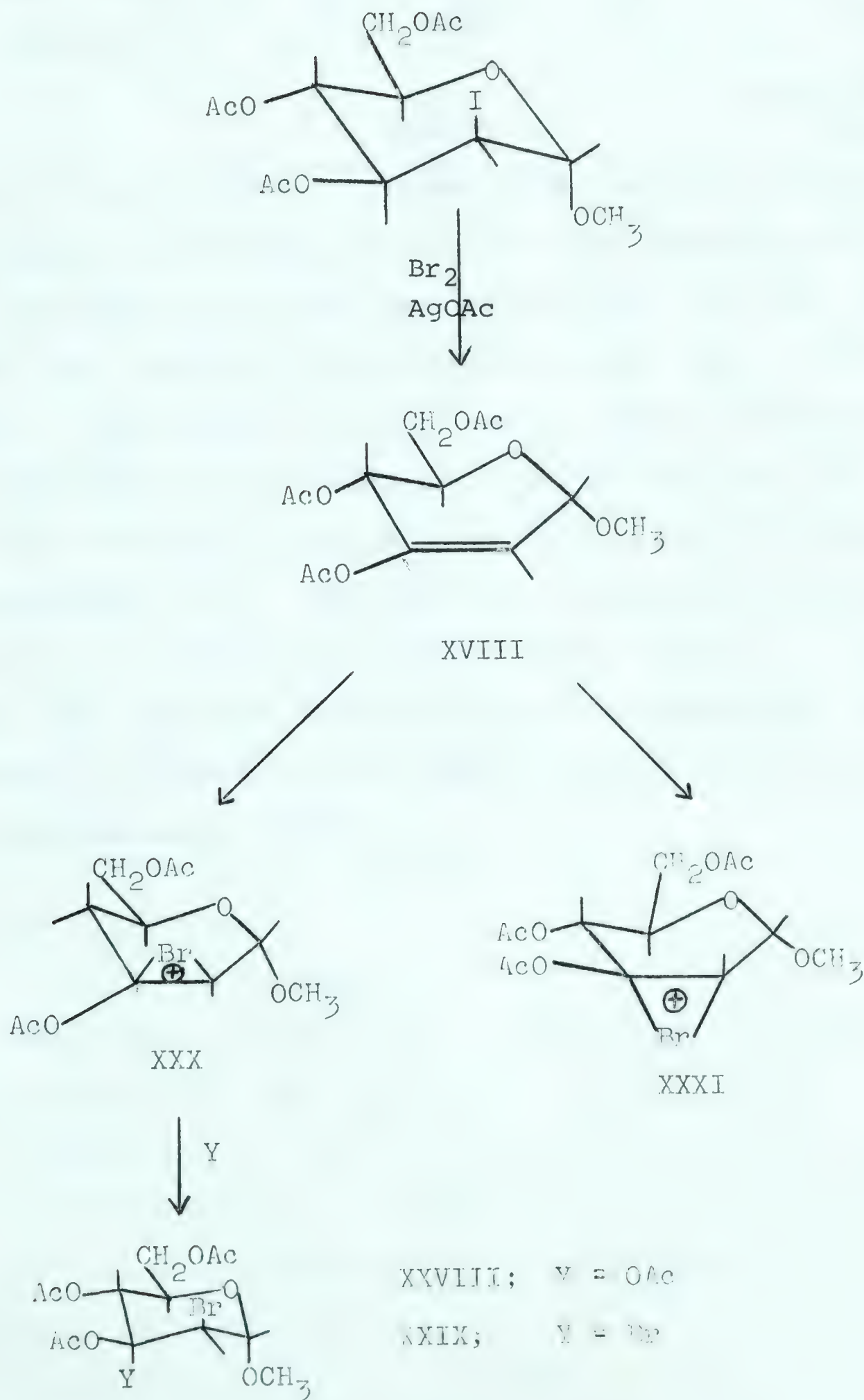
pyranoside (XVI), (35). This conversion requires the intermediary formation of methyl 2,3-anhydro- $\alpha$ -D-allopyranoside (XXVII) which undergoes oxide-ring migration (35) to form the 3,6-anhydro sugar.

It was, therefore, clearly apparent that the major product of brominolysis of the 2-iodo-mannoside was an acetylated derivative of the 3-ketose, methyl 2-bromo-2-deoxy- $\alpha$ -D-erythro-hexopyranoside-3-ulose, XVII. This compound, which appeared (n.m.r.) to make up about 60% of the reaction product, is in all likelihood (see the following paragraphs) the acylal, XXVIII. The alkaline conditions for sodium borohydride reduction (Scheme 9) would probably promote hydrolysis to the ketone before reduction to give the favored axial hydroxyl group (45) on carbon-3.

The course of brominolysis of cyclohexyl iodide (Scheme 5) had indicated that the main course of reaction of iodides of cyclic structures could involve elimination. In the case of the 2-iodo-mannoside this would lead (Scheme 10) to the enol acetate, XVIII, which would undergo acetoxy bromination to give XXVIII. The formation of the dibromide XXIX would be prevented by the formation of insoluble silver bromide. The axial 2-bromine of the 2-bromo-altroside XI indicates that the intermediate bromonium ion XXX predominated over the alternative XXXI, Scheme 11. The positive charge would be stabilized at carbon-3 by electron release from the ether-oxygen, and nucleophilic attack by the acetate ion now follows the favored course to trans-diaxial opening (45).

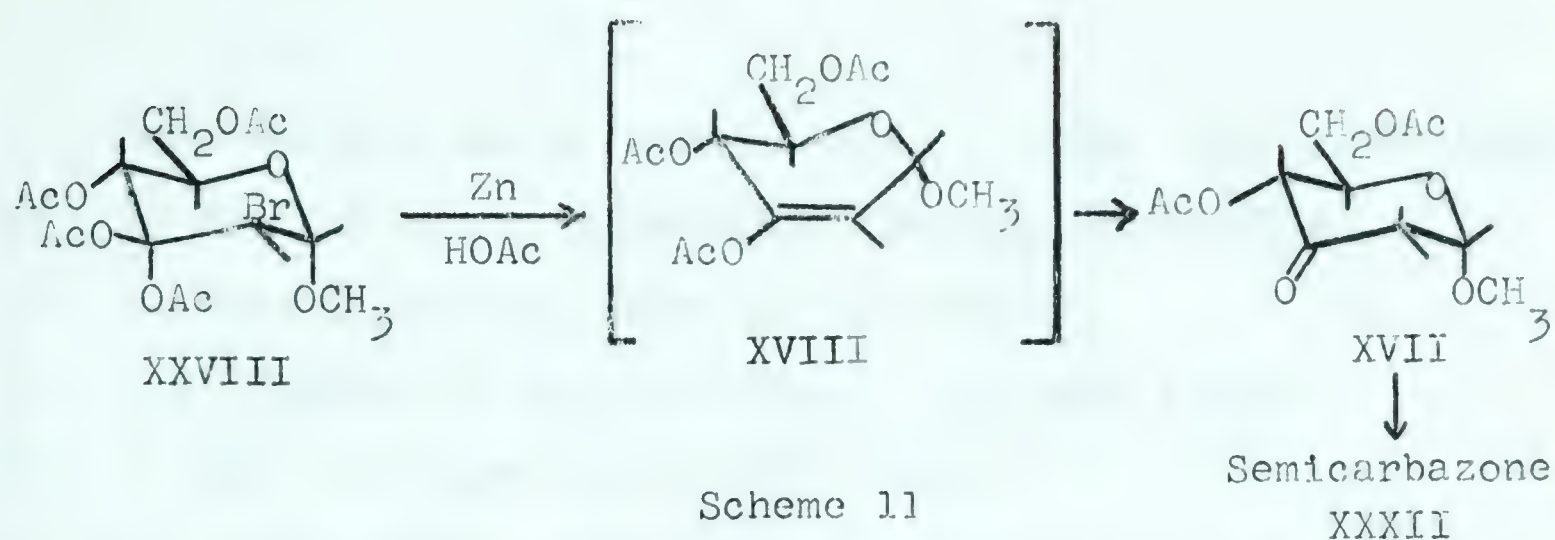
In order to confirm the structure for XXVIII, a sample of the crude product of brominolysis was reduced with zinc dust in acetic acid. Deacetoxybromination, Scheme 12, would lead to





Scheme 10





the enol acetate, XVIII, but the latter would not withstand the acid reaction conditions and would suffer hydrolysis to give the enol and thence the 3-keto derivative XVII. In fact, the reaction product was shown by infrared spectroscopy, Fig. 14, to be the ketone. The product was converted by sodium borohydride reduction with simultaneous deacetylation to a substance with the same  $R_f$  and color reactions as the above-mentioned methyl 2-deoxy- $\alpha$ -D-allopyranoside, XIV. When the crude product of the zinc dust reaction was treated with semicarbazide, Scheme 11, a crystalline product was deposited which possessed the elementary composition expected for methyl 4,6-di-O-acetyl-2-deoxy-3-oxo- $\alpha$ -D-glucopyranoside semicarbazone (XXXII).



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